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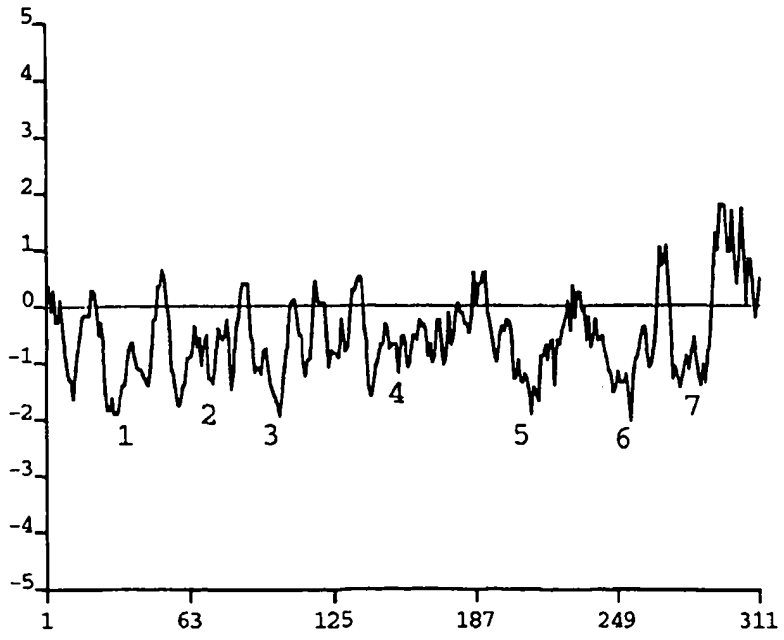
(54) Title: G-PROTEIN COUPLED RECEPTORS



(57) Abstract: The invention provides human G-protein coupled receptors (GCREC) and polynucleotides which identify and encode GCREC. The invention also provides expression vectors, host, cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with aberrant expression of GCREC.

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G-PROTEIN COUPLED RECEPTORS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of G-protein coupled receptors and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative, neurological, cardiovascular, gastrointestinal, autoimmune/inflammatory, and metabolic disorders, and viral infections, and in the assessment of the effects of exogenous compounds on the expression of nucleic acid and amino acid sequences of G-protein coupled receptors.

BACKGROUND OF THE INVENTION

Signal transduction is the general process by which cells respond to extracellular signals. Signal transduction across the plasma membrane begins with the binding of a signal molecule, e.g., a hormone, neurotransmitter, or growth factor, to a cell membrane receptor. The receptor, thus activated, triggers an intracellular biochemical cascade that ends with the activation of an intracellular target molecule, such as a transcription factor. This process of signal transduction regulates all types of cell functions including cell proliferation, differentiation, and gene transcription. The G-protein coupled receptors (GPCRs), encoded by one of the largest families of genes yet identified, play a central role in the transduction of extracellular signals across the plasma membrane. GPCRs have a proven history of being successful therapeutic targets.

GPCRs are integral membrane proteins characterized by the presence of seven hydrophobic transmembrane domains which together form a bundle of antiparallel alpha (α) helices. GPCRs range in size from under 400 to over 1000 amino acids (Strosberg, A.D. (1991) Eur. J. Biochem. 196:1-10; Coughlin, S.R. (1994) Curr. Opin. Cell Biol. 6:191-197). The amino-terminus of a GPCR is extracellular, is of variable length, and is often glycosylated. The carboxy-terminus is cytoplasmic and generally phosphorylated. Extracellular loops alternate with intracellular loops and link the transmembrane domains. Cysteine disulfide bridges linking the second and third extracellular loops may interact with agonists and antagonists. The most conserved domains of GPCRs are the transmembrane domains and the first two cytoplasmic loops. The transmembrane domains account, in part, for structural and functional features of the receptor. In most cases, the bundle of α helices forms a ligand-binding pocket. The extracellular N-terminal segment, or one or more of the three extracellular loops, may also participate in ligand binding. Ligand binding activates the receptor by inducing a conformational change in intracellular portions of the receptor. In turn, the large, third intracellular loop of the activated receptor interacts with a heterotrimeric guanine nucleotide binding (G) protein complex which mediates further intracellular signaling activities, including the activation of second

messengers such as cyclic AMP (cAMP), phospholipase C, and inositol triphosphate, and the interaction of the activated GPCR with ion channel proteins. (See, e.g., Watson, S. and S. Arkinstall (1994) The G-protein Linked Receptor Facts Book, Academic Press, San Diego CA, pp. 2-6; Bolander, F.F. (1994) Molecular Endocrinology, Academic Press, San Diego CA, pp. 162-176; Baldwin, J.M. (1994) Curr. Opin. Cell Biol. 6:180-190.)

GPCRs include receptors for sensory signal mediators (e.g., light and olfactory stimulatory molecules); adenosine, γ-aminobutyric acid (GABA), hepatocyte growth factor, melanocortins, neuropeptide Y, opioid peptides, opsins, somatostatin, tachykinins, vasoactive intestinal polypeptide family, and vasopressin; biogenic amines (e.g., dopamine, epinephrine and norepinephrine, histamine, glutamate (metabotropic effect), acetylcholine (muscarinic effect), and serotonin); chemokines; lipid mediators of inflammation (e.g., prostaglandins and prostanoids, platelet activating factor, and leukotrienes); and peptide hormones (e.g., bombesin, bradykinin, calcitonin, C5a anaphylatoxin, endothelin, follicle-stimulating hormone (FSH), gonadotropic-releasing hormone (GnRH), neurokinin, and thyrotropin-releasing hormone (TRH), and oxytocin). GPCRs which act as receptors for stimuli that have yet to be identified are known as orphan receptors.

The diversity of the GPCR family is further increased by alternative splicing. Many GPCR genes contain introns, and there are currently over 30 such receptors for which splice variants have been identified. The largest number of variations are at the protein C-terminus. N-terminal and cytoplasmic loop variants are also frequent, while variants in the extracellular loops or transmembrane domains are less common. Some receptors have more than one site at which variance can occur. The splicing variants appear to be functionally distinct, based upon observed differences in distribution, signaling, coupling, regulation, and ligand binding profiles (Kilpatrick, G.J. et al. (1999) Trends Pharmacol. Sci. 20:294-301).

GPCRs can be divided into three major subfamilies: the rhodopsin-like, secretin-like, and metabotropic glutamate receptor subfamilies. Members of these GPCR subfamilies share similar functions and the characteristic seven transmembrane structure, but have divergent amino acid sequences. The largest family consists of the rhodopsin-like GPCRs, which transmit diverse extracellular signals including hormones, neurotransmitters, and light. Rhodopsin is a photosensitive GPCR found in animal retinas. In vertebrates, rhodopsin molecules are embedded in membranous stacks found in photoreceptor (rod) cells. Each rhodopsin molecule responds to a photon of light by triggering a decrease in cGMP levels which leads to the closure of plasma membrane sodium channels. In this manner, a visual signal is converted to a neural impulse. Other rhodopsin-like GPCRs are directly involved in responding to neurotransmitters. These GPCRs include the receptors for adrenaline (adrenergic receptors), acetylcholine (muscarinic receptors), adenosine, galanin, and glutamate (N-

methyl-D-aspartate/NMDA receptors). (Reviewed in Watson, S. and S. Arkinstall (1994) The G-Protein Linked Receptor Facts Book, Academic Press, San Diego CA, pp. 7-9, 19-22, 32-35, 130-131, 214-216, 221-222; Habert-Ortoli, E. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9780-9783.)

The galanin receptors mediate the activity of the neuroendocrine peptide galanin, which inhibits secretion of insulin, acetylcholine, serotonin and noradrenaline, and stimulates prolactin and growth hormone release. Galanin receptors are involved in feeding disorders, pain, depression, and Alzheimer's disease (Kask, K. et al. (1997) Life Sci. 60:1523-1533). Other nervous system rhodopsin-like GPCRs include a growing family of receptors for lysophosphatidic acid and other lysophospholipids, which appear to have roles in development and neuropathology (Chun, J. et al. (1999) Cell Biochem. Biophys. 30:213-242).

The largest subfamily of GPCRs, the olfactory receptors, are also members of the rhodopsin-like GPCR family. These receptors function by transducing odorant signals. Numerous distinct olfactory receptors are required to distinguish different odors. Each olfactory sensory neuron expresses only one type of olfactory receptor, and distinct spatial zones of neurons expressing distinct receptors are found in nasal passages. For example, the RA1c receptor which was isolated from a rat brain library, has been shown to be limited in expression to very distinct regions of the brain and a defined zone of the olfactory epithelium (Raming, K. et al. (1998) Receptors Channels 6:141-151). However, the expression of olfactory-like receptors is not confined to olfactory tissues. For example, three rat genes encoding olfactory-like receptors having typical GPCR characteristics showed expression patterns not only in taste and olfactory tissue, but also in male reproductive tissue (Thomas, M.B. et al. (1996) Gene 178:1-5).

Members of the secretin-like GPCR subfamily have as their ligands peptide hormones such as secretin, calcitonin, glucagon, growth hormone-releasing hormone, parathyroid hormone, and vasoactive intestinal peptide. For example, the secretin receptor responds to secretin, a peptide hormone that stimulates the secretion of enzymes and ions in the pancreas and small intestine (Watson, supra, pp. 278-283). Secretin receptors are about 450 amino acids in length and are found in the plasma membrane of gastrointestinal cells. Binding of secretin to its receptor stimulates the production of cAMP.

Examples of secretin-like GPCRs implicated in inflammation and the immune response include the EGF module-containing, mucin-like hormone receptor (Emr1) and CD97 receptor proteins. These GPCRs are members of the recently characterized EGF-TM7 receptors subfamily. These seven transmembrane hormone receptors exist as heterodimers in vivo and contain between three and seven potential calcium-binding EGF-like motifs. CD97 is predominantly expressed in leukocytes and is markedly upregulated on activated B and T cells (McKnight, A.J. and S. Gordon (1998) J. Leukoc. Biol. 63:271-280).

The third GPCR subfamily is the metabotropic glutamate receptor family. Glutamate is the major excitatory neurotransmitter in the central nervous system. The metabotropic glutamate receptors modulate the activity of intracellular effectors, and are involved in long-term potentiation (Watson, supra, p.130). The Ca^{2+}-sensing receptor, which senses changes in the extracellular concentration of calcium ions, has a large extracellular domain including clusters of acidic amino acids which may be involved in calcium binding. The metabotropic glutamate receptor family also includes pheromone receptors, the $GABA_B$ receptors, and the taste receptors.

Other subfamilies of GPCRs include two groups of chemoreceptor genes found in the nematodes Caenorhabditis elegans and Caenorhabditis briggsae, which are distantly related to the mammalian olfactory receptor genes. The yeast pheromone receptors STE2 and STE3, involved in the response to mating factors on the cell membrane, have their own seven-transmembrane signature, as do the cAMP receptors from the slime mold Dictyostelium discoideum, which are thought to regulate the aggregation of individual cells and control the expression of numerous developmentally-regulated genes.

GPCR mutations, which may cause loss of function or constitutive activation, have been associated with numerous human diseases (Coughlin, supra). For instance, retinitis pigmentosa may arise from mutations in the rhodopsin gene. Furthermore, somatic activating mutations in the thyrotropin receptor have been reported to cause hyperfunctioning thyroid adenomas, suggesting that certain GPCRs susceptible to constitutive activation may behave as protooncogenes (Parma, J. et al. (1993) Nature 365:649-651). GPCR receptors for the following ligands also contain mutations associated with human disease: luteinizing hormone (precocious puberty); vasopressin V_2 (X-linked nephrogenic diabetes); glucagon (diabetes and hypertension); calcium (hyperparathyroidism, hypocalcuria, hypercalcemia); parathyroid hormone (short limbed dwarfism); β_3-adrenoceptor (obesity, non-insulin-dependent diabetes mellitus); growth hormone releasing hormone (dwarfism); and adrenocorticotropin (glucocorticoid deficiency) (Wilson, S. et al. (1998) Br. J. Pharmocol. 125:1387-1392; Stadel, J.M. et al. (1997) Trends Pharmacol. Sci. 18:430-437). GPCRs are also involved in depression, schizophrenia, sleeplessness, hypertension, anxiety, stress, renal failure, and several cardiovascular disorders (Horn, F. and G. Vriend (1998) J. Mol. Med. 76:464-468).

In addition, within the past 20 years several hundred new drugs have been recognized that are directed towards activating or inhibiting GPCRs. The therapeutic targets of these drugs span a wide range of diseases and disorders, including cardiovascular, gastrointestinal, and central nervous system disorders as well as cancer, osteoporosis and endometriosis (Wilson, supra; Stadel, supra). For example, the dopamine agonist L-dopa is used to treat Parkinson's disease, while a dopamine antagonist is used to treat schizophrenia and the early stages of Huntington's disease. Agonists and antagonists of adrenoceptors have been used for the treatment of asthma, high blood pressure, other cardiovascular

disorders, and anxiety; muscarinic agonists are used in the treatment of glaucoma and tachycardia; serotonin 5HT1D antagonists are used against migraine; and histamine H1 antagonists are used against allergic and anaphylactic reactions, hay fever, itching, and motion sickness (Horn, supra).

Recent research suggests potential future therapeutic uses for GPCRs in the treatment of metabolic disorders including diabetes, obesity, and osteoporosis. For example, mutant V2 vasopressin receptors causing nephrogenic diabetes could be functionally rescued in vitro by co-expression of a C-terminal V2 receptor peptide spanning the region containing the mutations. This result suggests a possible novel strategy for disease treatment (Schöneberg, T. et al. (1996) EMBO J. 15:1283-1291). Mutations in melanocortin-4 receptor (MC4R) are implicated in human weight regulation and obesity. As with the vasopressin V2 receptor mutants, these MC4R mutants are defective in trafficking to the plasma membrane (Ho, G. and R.G. MacKenzie (1999) J. Biol. Chem. 274:35816-35822), and thus might be treated with a similar strategy. The type 1 receptor for parathyroid hormone (PTH) is a GPCR that mediates the PTH-dependent regulation of calcium homeostasis in the bloodstream. Study of PTH/receptor interactions may enable the development of novel PTH receptor ligands for the treatment of osteoporosis (Mannstadt, M. et al. (1999) Am. J. Physiol. 277:F665-F675).

The chemokine receptor group of GPCRs have potential therapeutic utility in inflammation and infectious disease. (For review, see Locati, M. and P.M. Murphy (1999) Annu. Rev. Med. 50:425-440.) Chemokines are small polypeptides that act as intracellular signals in the regulation of leukocyte trafficking, hematopoiesis, and angiogenesis. Targeted disruption of various chemokine receptors in mice indicates that these receptors play roles in pathologic inflammation and in autoimmune disorders such as multiple sclerosis. Chemokine receptors are also exploited by infectious agents, including herpesviruses and the human immunodeficiency virus (HIV-1) to facilitate infection. A truncated version of chemokine receptor CCR5, which acts as a coreceptor for infection of T-cells by HIV-1, results in resistance to AIDS, suggesting that CCR5 antagonists could be useful in preventing the development of AIDS.

The discovery of new G-protein coupled receptors and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative, neurological, cardiovascular, gastrointestinal, autoimmune/inflammatory, and metabolic disorders, and viral infections, and in the assessment of the effects of exogenous compounds on the expression of nucleic acid and amino acid sequences of G-protein coupled receptors.

SUMMARY OF THE INVENTION

The invention features purified polypeptides, G-protein coupled receptors, referred to

collectively as "GCREC" and individually as "GCREC-1," "GCREC-2," "GCREC-3," "GCREC-4," "GCREC-5," "GCREC-6," "GCREC-7," "GCREC-8," "GCREC-9," "GCREC-10," "GCREC-11," "GCREC-12," "GCREC-13," "GCREC-14," "GCREC-15," "GCREC-16," "GCREC-17," "GCREC-18," "GCREC-19," "GCREC-20," "GCREC-21," "GCREC-22," "GCREC-23," "GCREC-24," "GCREC-25," "GCREC-26," "GCREC-27," "GCREC-28," "GCREC-29," "GCREC-30," "GCREC-31," "GCREC-32," "GCREC-33," "GCREC-34," "GCREC-35," "GCREC-36," "GCREC-37," "GCREC-38," and "GCREC-39." In one aspect, the invention provides an isolated polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-39.

The invention further provides an isolated polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-39. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:40-78.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising an amino acid

sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39.

The invention further provides an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and

optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

The invention further provides a composition comprising an effective amount of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and a pharmaceutically acceptable excipient. In one embodiment, the composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional GCREC, comprising administering to a patient in need of such treatment the composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional GCREC, comprising administering to a patient in need of such treatment the composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional GCREC, comprising administering to a patient in need of such treatment the composition.

The invention further provides a method of screening for a compound that specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the activity of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the

activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:40-78, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound; b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, ii) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, ii) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide comprises a fragment of a polynucleotide sequence selected from the group consisting of i)-v) above; c) quantifying the amount of hybridization complex; and d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

BRIEF DESCRIPTION OF THE FIGURES AND TABLES

Figure 1 shows the hydrophobicity plot for GCREC-1 (SEQ ID NO:1; Incyte ID number 104941CD1). The hydrophobicity plot was generated using the MacDNASIS Pro software. The positive X axis reflects amino acid position, and the negative Y axis, hydrophobicity. The numbers indicate the positions of predicted transmembrane domains.

Figure 2 shows the hydrophobicity plot for GCREC-3 (SEQ ID NO:3; Incyte ID number 3168839CD1).

Figure 3 shows the hydrophobicity plot for GCREC-4 (SEQ ID NO:4; Incyte ID number 3291235CD1).

Figure 4 shows the hydrophobicity plot for GCREC-5 (SEQ ID NO:5; Incyte ID number 7472001CD1).

Figure 5 shows the hydrophobicity plot for GCREC-6 (SEQ ID NO:6; Incyte ID number 7472003CD1).

Figure 6 shows the hydrophobicity plot for GCREC-7 (SEQ ID NO:7; Incyte ID number 7472004CD1).

Figure 7 shows the hydrophobicity plot for GCREC-19 (SEQ ID NO:19; Incyte ID number 3068234CD1).

Figure 8 shows the hydrophobicity plot for GCREC-20 (SEQ ID NO:20; Incyte ID number 5029478CD1).

Figure 9 shows the hydrophobicity plot for GCREC-21 (SEQ ID NO:21; Incyte ID number 5102576CD1).

Table 1 summarizes the nomenclature for the polynucleotide and polypeptide sequences of the present invention.

Table 2 shows the GenBank identification number and annotation of the nearest GenBank homolog for each polypeptide of the invention. The probability score for the match between each polypeptide and its GenBank homolog is also shown.

Table 3 shows structural features of each polypeptide sequence, including predicted motifs and domains, along with the methods, algorithms, and searchable databases used for analysis of each polypeptide.

Table 4 lists the cDNA and genomic DNA fragments which were used to assemble each polynucleotide sequence, along with selected fragments of the polynucleotide sequences.

Table 5 shows the representative cDNA library for each polynucleotide of the invention.

Table 6 provides an appendix which describes the tissues and vectors used for construction of the cDNA libraries shown in Table 5.

Table 7 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing

particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"GCREC" refers to the amino acid sequences of substantially purified GCREC obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of GCREC. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of GCREC either by directly interacting with GCREC or by acting on components of the biological pathway in which GCREC participates.

An "allelic variant" is an alternative form of the gene encoding GCREC. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding GCREC include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as GCREC or a polypeptide with at least one functional characteristic of GCREC. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of

the polynucleotide encoding GCREC, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding GCREC. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent GCREC. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of GCREC is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of GCREC. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of GCREC either by directly interacting with GCREC or by acting on components of the biological pathway in which GCREC participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, $F(ab')_2$, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind GCREC polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that

makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic" refers to the capability of the natural, recombinant, or synthetic GCREC, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement, 3'-TCA-5'.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding GCREC or fragments of GCREC may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (Applied Biosystems,

Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

Original Residue	Conservative Substitution
Ala	Gly, Ser
Arg	His, Lys
Asn	Asp, Gln, His
Asp	Asn, Glu
Cys	Ala, Ser
Gln	Asn, Glu, His
Glu	Asp, Gln, His
Gly	Ala
His	Asn, Arg, Gln, Glu
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile
Phe	His, Met, Leu, Trp, Tyr
Ser	Cys, Thr
Thr	Ser, Val
Trp	Phe, Tyr
Tyr	His, Phe, Trp
Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. Chemical modifications of a polynucleotide can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified

by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

A "fragment" is a unique portion of GCREC or the polynucleotide encoding GCREC which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50%) of a polypeptide as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:40-78 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:40-78, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:40-78 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:40-78 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:40-78 and the region of SEQ ID NO:40-78 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-39 is encoded by a fragment of SEQ ID NO:40-78. A fragment of SEQ ID NO:1-39 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-39. For example, a fragment of SEQ ID NO:1-39 is useful as an immunogenic peptide

The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequences.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at http://www.ncbi.nlm.nih.gov/BLAST/. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at http://www.ncbi.nlm.nih.gov/gorf/bl2.html. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

Penalty for mismatch: -2

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 11

Filter: on

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Open Gap: 11 and Extension Gap: 1 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 3

Filter: on

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size and which contain all of the elements required for chromosome replication, segregation and maintenance.

The term "humanized antibody" refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention

include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 μg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of GCREC which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of GCREC which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides, polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

The term "modulate" refers to a change in the activity of GCREC. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of GCREC.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide,

polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Post-translational modification" of an GCREC may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of GCREC.

"Probe" refers to nucleic acid sequences encoding GCREC, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al. (1987) Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al. (1990) PCR

Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be use to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription, translation, or RNA stability.

"Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid, amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing GCREC, nucleic acids encoding GCREC, or fragments thereof may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acid residues or nucleotides by different amino acid residues or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers,

microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

A "transcript image" refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

"Transformation" describes a process by which exogenous DNA is introduced into a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed cells" includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "transgenic organism," as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, plants and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989), supra.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternative splicing of exons during mRNA processing. The corresponding polypeptide may

possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides will generally have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

The invention is based on the discovery of new human G-protein coupled receptors (GCREC), the polynucleotides encoding GCREC, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, neurological, cardiovascular, gastrointestinal, autoimmune/inflammatory, and metabolic disorders, and viral infections.

Table 1 summarizes the nomenclature for the polynucleotide and polypeptide sequences of the invention. Each polynucleotide and its corresponding polypeptide are correlated to a single Incyte project identification number (Incyte Project ID). Each polypeptide sequence is denoted by both a polypeptide sequence identification number (Polypeptide SEQ ID NO:) and an Incyte polypeptide sequence number (Incyte Polypeptide ID) as shown. Each polynucleotide sequence is denoted by both a polynucleotide sequence identification number (Polynucleotide SEQ ID NO:) and an Incyte polynucleotide consensus sequence number (Incyte Polynucleotide ID) as shown.

Table 2 shows sequences with homology to the polypeptides of the invention as identified by BLAST analysis against the GenBank protein (genpept) database. Columns 1 and 2 show the polypeptide sequence identification number (Polypeptide SEQ ID NO:) and the corresponding Incyte polypeptide sequence number (Incyte Polypeptide ID) for each polypeptide of the invention. Column 3 shows the GenBank identification number (Genbank ID NO:) of the nearest GenBank homolog. Column 4 shows the probability score for the match between each polypeptide and its GenBank homolog. Column 5 shows the annotation of the GenBank homolog along with relevant citations where applicable, all of which are expressly incorporated by reference herein.

Table 3 shows various structural features of each of the polypeptides of the invention. Columns

1 and 2 show the polypeptide sequence identification number (SEQ ID NO:) and the corresponding Incyte polypeptide sequence number (Incyte Polypeptide ID) for each polypeptide of the invention. Column 3 shows the number of amino acid residues in each polypeptide. Column 4 shows potential phosphorylation sites, and column 5 shows potential glycosylation sites, as determined by the MOTIFS program of the GCG sequence analysis software package (Genetics Computer Group, Madison WI). Column 6 shows amino acid residues comprising signature sequences, domains, and motifs. Column 7 shows analytical methods for protein structure/function analysis and in some cases, searchable databases to which the analytical methods were applied.

As shown in Table 4, the polynucleotide sequences of the present invention were assembled using cDNA sequences or coding (exon) sequences derived from genomic DNA, or any combination of these two types of sequences. Columns 1 and 2 list the polynucleotide sequence identification number (Polynucleotide SEQ ID NO:) and the corresponding Incyte polynucleotide consensus sequence number (Incyte Polynucleotide ID) for each polynucleotide of the invention. Column 3 shows the length of each polynucleotide sequence in basepairs. Column 4 lists fragments of the polynucleotide sequences which are useful, for example, in hybridization or amplification technologies that identify SEQ ID NO:40-78 or that distinguish between SEQ ID NO:40-78 and related polynucleotide sequences. Column 5 shows identification numbers corresponding to cDNA sequences, coding sequences (exons) predicted from genomic DNA, and/or sequence assemblages comprised of both cDNA and genomic DNA. These sequences were used to assemble the polynucleotide sequences of the invention. Columns 6 and 7 of Table 4 show the nucleotide start (5') and stop (3') positions of the cDNA and genomic sequences in column 5 relative to their respective sequences.

The identification numbers in Column 5 of Table 4 may refer specifically, for example, to Incyte cDNAs along with their corresponding cDNA libraries. For example, 927003T6 is the identification number of an Incyte cDNA sequence, and BRAINOT04 is the cDNA library from which it is derived. Incyte cDNAs for which cDNA libraries are not indicated were derived from pooled cDNA libraries (e.g., 70489898V1). Alternatively, the identification numbers in column 5 may refer to GenBank cDNAs or ESTs (e.g., g835247) which contributed to the assembly of the polynucleotide sequences. Alternatively, the identification numbers in column 5 may refer to coding regions predicted by Genscan analysis of genomic DNA. For example, g4190944.v113.gs_10.edit is the identification number of a Genscan-predicted coding sequence, with g4190944 being the GenBank identification number of the sequence to which Genscan was applied. The Genscan-predicted coding sequences may have been edited prior to assembly. (See Example IV.) Alternatively, the identification numbers in column 5 may refer to assemblages of both cDNA and Genscan-predicted exons brought together by an "exon stitching" algorithm. (See Example V.) Alternatively, the identification numbers in column 5

may refer to assemblages of both cDNA and Genscan-predicted exons brought together by an "exon-stretching" algorithm. (See Example V.) In some cases, Incyte cDNA coverage redundant with the sequence coverage shown in column 5 was obtained to confirm the final consensus polynucleotide sequence, but the relevant Incyte cDNA identification numbers are not shown.

Table 5 shows the representative cDNA libraries for those polynucleotide sequences which were assembled using Incyte cDNA sequences. The representative cDNA library is the Incyte cDNA library which is most frequently represented by the Incyte cDNA sequences which were used to assemble and confirm the above polynucleotide sequences. The tissues and vectors which were used to construct the cDNA libraries shown in Table 5 are described in Table 6.

The invention also encompasses GCREC variants. A preferred GCREC variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the GCREC amino acid sequence, and which contains at least one functional or structural characteristic of GCREC.

The invention also encompasses polynucleotides which encode GCREC. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:40-78, which encodes GCREC. The polynucleotide sequences of SEQ ID NO:40-78, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding GCREC. In particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding GCREC. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:40-78 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:40-78. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of GCREC.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding GCREC, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally

occurring GCREC, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode GCREC and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring GCREC under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding GCREC or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding GCREC and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode GCREC and GCREC derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding GCREC or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:40-78 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Applied Biosystems), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Applied Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Applied Biosystems), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols

in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding GCREC may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 primer analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Applied Biosystems), and the entire

process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode GCREC may be cloned in recombinant DNA molecules that direct expression of GCREC, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express GCREC.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter GCREC-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 17:259-264; and Crameri, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of GCREC, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

In another embodiment, sequences encoding GCREC may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.) Alternatively, GCREC itself or a fragment thereof may be synthesized using chemical methods. For example, peptide

synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY, pp.55-60; and Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Applied Biosystems). Additionally, the amino acid sequence of GCREC, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, supra, pp. 28-53.)

In order to express a biologically active GCREC, the nucleotide sequences encoding GCREC or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding GCREC. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding GCREC. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding GCREC and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding GCREC and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding GCREC. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509; Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu, N. (1987) EMBO J. 6:307-311; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.) Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al. (1993) Proc. Natl. Acad. Sci. USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al. (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M. and N. Somia (1997) Nature 389:239-242.) The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding GCREC. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding GCREC can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding GCREC into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of GCREC are needed, e.g. for the production of antibodies, vectors which direct high level expression of GCREC may be used. For example, vectors containing the strong, inducible SP6 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of GCREC. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra;

Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; and Scorer, C.A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of GCREC. Transcription of sequences encoding GCREC may be driven by viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding GCREC may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses GCREC in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of GCREC in cell lines is preferred. For example, sequences encoding GCREC can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase

genes, for use in *tk*⁻ and *apr*⁻ cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate ß-glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding GCREC is inserted within a marker gene sequence, transformed cells containing sequences encoding GCREC can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding GCREC under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding GCREC and that express GCREC may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of GCREC using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on GCREC is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding GCREC include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding GCREC, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a varicty of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding GCREC may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode GCREC may be designed to contain signal sequences which direct secretion of GCREC through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding GCREC may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric GCREC protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of GCREC activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose

binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the GCREC encoding sequence and the heterologous protein sequence, so that GCREC may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled GCREC may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ^{35}S-methionine.

GCREC of the present invention or fragments thereof may be used to screen for compounds that specifically bind to GCREC. At least one and up to a plurality of test compounds may be screened for specific binding to GCREC. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

In one embodiment, the compound thus identified is closely related to the natural ligand of GCREC, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, e.g., Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which GCREC binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the compound can be rationally designed using known techniques. In one embodiment, screening for these compounds involves producing appropriate cells which express GCREC, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing GCREC or cell membrane fractions which contain GCREC are then contacted with a test compound and binding, stimulation, or inhibition of activity of either GCREC or the compound is analyzed.

An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with GCREC, either in solution or affixed to a solid support, and detecting the binding of GCREC to the compound. Alternatively, the assay may detect or measure binding of a test compound in the presence of a

labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

GCREC of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of GCREC. Such compounds may include agonists, antagonists, or partial or inverse agonists. In one embodiment, an assay is performed under conditions permissive for GCREC activity, wherein GCREC is combined with at least one test compound, and the activity of GCREC in the presence of a test compound is compared with the activity of GCREC in the absence of the test compound. A change in the activity of GCREC in the presence of the test compound is indicative of a compound that modulates the activity of GCREC. Alternatively, a test compound is combined with an in vitro or cell-free system comprising GCREC under conditions suitable for GCREC activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of GCREC may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding GCREC or their mammalian homologs may be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent Number 5,175,383 and U.S. Patent Number 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding GCREC may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

Polynucleotides encoding GCREC can also be used to create "knockin" humanized animals

(pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding GCREC is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress GCREC, e.g., by secreting GCREC in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-74).

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of GCREC and G-protein coupled receptors. In addition, the expression of GCREC is closely associated with cancerous, neurological, gastrointestinal, and lung tissue. Therefore, GCREC appears to play a role in cell proliferative, neurological, cardiovascular, gastrointestinal, autoimmune/inflammatory, and metabolic disorders, and viral infections. In the treatment of disorders associated with increased GCREC expression or activity, it is desirable to decrease the expression or activity of GCREC. In the treatment of disorders associated with decreased GCREC expression or activity, it is desirable to increase the expression or activity of GCREC.

Therefore, in one embodiment, GCREC or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GCREC. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental

retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, Tourette's disorder, progressive supranuclear palsy, corticobasal degeneration, and familial frontotemporal dementia; a cardiovascular disorder such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, vascular tumors, complications of thrombolysis, balloon angioplasty, vascular replacement, and coronary artery bypass graft surgery, congestive heart failure, ischemic heart disease, angina pectoris, myocardial infarction, hypertensive heart disease, degenerative valvular heart disease, calcific aortic valve stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, congenital heart disease, and complications of cardiac transplantation; a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, alpha$_1$-antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hepatic tumors including nodular hyperplasias, adenomas, and carcinomas; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal

dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a metabolic disorder such as diabetes, obesity, and osteoporosis; and an infection by a viral agent classified as adenovirus, arenavirus, bunyavirus, calicivirus, coronavirus, filovirus, hepadnavirus, herpesvirus, flavivirus, orthomyxovirus, parvovirus, papovavirus, paramyxovirus, picornavirus, poxvirus, reovirus, retrovirus, rhabdovirus, and togavirus.

In another embodiment, a vector capable of expressing GCREC or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GCREC including, but not limited to, those described above.

In a further embodiment, a composition comprising a substantially purified GCREC in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GCREC including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of GCREC may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of GCREC including, but not limited to, those listed above.

In a further embodiment, an antagonist of GCREC may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of GCREC. Examples of such disorders include, but are not limited to, those cell proliferative, neurological, cardiovascular, gastrointestinal, autoimmune/inflammatory, and metabolic disorders, and viral infections, described above. In one aspect, an antibody which specifically binds GCREC may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express GCREC.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding GCREC may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of GCREC including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary

sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of GCREC may be produced using methods which are generally known in the art. In particular, purified GCREC may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind GCREC. Antibodies to GCREC may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with GCREC or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to GCREC have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of GCREC amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to GCREC may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate

antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce GCREC-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for GCREC may also be generated. For example, such fragments include, but are not limited to, $F(ab')_2$ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between GCREC and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering GCREC epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for GCREC. Affinity is expressed as an association constant, K_a, which is defined as the molar concentration of GCREC-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple GCREC epitopes, represents the average affinity, or avidity, of the antibodies for GCREC. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular GCREC epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the GCREC-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a

ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of GCREC, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of GCREC-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding GCREC, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding GCREC. Such technology is well known in the art, and antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding GCREC. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) J. Allergy Cli. Immunol. 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) Blood 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) Pharmacol. Ther. 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) Br. Med. Bull. 51(1):217-225; Boado, R.J. et al. (1998) J. Pharm. Sci. 87(11):1308-1315; and Morris, M.C. et al. (1997) Nucleic Acids Res. 25(14):2730-2736.)

In another embodiment of the invention, polynucleotides encoding GCREC may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) Science 288:669-672), severe combined

immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475), cystic fibrosis (Zabner, J. et al. (1993) Cell 75:207-216; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), thalassamias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) Science 270:404-410; Verma, I.M. and N. Somia (1997) Nature 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA. 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in GCREC expression or regulation causes disease, the expression of GCREC from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in GCREC are treated by constructing mammalian expression vectors encoding GCREC and introducing these vectors by mechanical means into GCREC-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev. Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and H. Récipon (1998) Curr. Opin. Biotechnol. 9:445-450).

Expression vectors that may be effective for the expression of GCREC include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). GCREC may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or β-actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. U.S.A. 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V.

and Blau, H.M. supra)), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding GCREC from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (1982) EMBO J. 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to GCREC expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding GCREC under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. Natl. Acad. Sci. U.S.A. 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and A.D. Miller (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., $CD4^+$ T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:7020-7029; Bauer, G. et al. (1997) Blood 89:2259-2267; Bonyhadi, M.L. (1997) J. Virol. 71:4707-4716; Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. U.S.A. 95:1201-1206; Su, L. (1997) Blood 89:2283-2290).

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding GCREC to cells which have one or more genetic abnormalities with respect to the expression of GCREC. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas

(Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annu. Rev. Nutr. 19:511-544 and Verma, I.M. and N. Somia (1997) Nature 18:389:239-242, both incorporated by reference herein.

In another alternative, a herpes-based, gene therapy delivery system is used to deliver polynucleotides encoding GCREC to target cells which have one or more genetic abnormalities with respect to the expression of GCREC. The use of herpes simplex virus (HSV)-based vectors may be especially valuable for introducing GCREC to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) Exp. Eye Res.169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) J. Virol. 73:519-532 and Xu, H. et al. (1994) Dev. Biol. 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus sequences, the generation of recombinant virus following the transfection of multiple plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to deliver polynucleotides encoding GCREC to target cells. The biology of the prototypic alphavirus, Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on the SFV genome (Garoff, H. and K.-J. Li (1998) Curr. Opin. Biotechnol. 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease and polymerase). Similarly, inserting the coding sequence for GCREC into the alphavirus genome in place of the capsid-coding region results in the production of a large number of GCREC-coding RNAs and the synthesis of high levels of GCREC in vector transduced cells. While alphavirus

infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of GCREC into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding GCREC.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding GCREC. Such DNA sequences may be incorporated into a wide variety of vectors with

suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding GCREC. Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-macromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased GCREC expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding GCREC may be therapeutically useful, and in the treament of disorders associated with decreased GCREC expression or activity, a compound which specifically promotes expression of the polynucleotide encoding GCREC may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective in altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a library of chemical compounds created combinatorially or randomly. A sample comprising a polynucleotide encoding GCREC is exposed to at least one test compound thus obtained. The sample may comprise, for example, an intact or permeabilized cell, or an in vitro cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding GCREC are assayed by any method commonly known in the art. Typically, the expression of a specific nucleotide is detected by hybridization with a probe having a nucleotide sequence complementary to the sequence of the polynucleotide encoding GCREC. The amount of hybridization may be quantified, thus

forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of the polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide can be carried out, for example, using a Schizosaccharomyces pombe gene expression system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Arndt, G.M. et al. (2000) Nucleic Acids Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruice, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruice, T.W. et al. (2000) U.S. Patent No. 6,022,691).

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such compositions may consist of GCREC, antibodies to GCREC, and mimetics, agonists, antagonists, or inhibitors of GCREC.

The compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

Compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins),

recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton. J.S. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

Compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

Specialized forms of compositions may be prepared for direct intracellular delivery of macromolecules comprising GCREC or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, GCREC or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example GCREC or fragments thereof, antibodies of GCREC, and agonists, antagonists or inhibitors of GCREC, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity

of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind GCREC may be used for the diagnosis of disorders characterized by expression of GCREC, or in assays to monitor patients being treated with GCREC or agonists, antagonists, or inhibitors of GCREC. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for GCREC include methods which utilize the antibody and a label to detect GCREC in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring GCREC, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of GCREC expression. Normal or standard values for GCREC expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibodies to GCREC under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of GCREC expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding GCREC may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of GCREC may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of GCREC, and to monitor regulation of GCREC levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding GCREC or closely related molecules may be used to identify nucleic acid sequences which encode GCREC. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding GCREC, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the GCREC encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:40-78 or from genomic sequences including promoters, enhancers, and introns of the GCREC gene.

Means for producing specific hybridization probes for DNAs encoding GCREC include the cloning of polynucleotide sequences encoding GCREC or GCREC derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding GCREC may be used for the diagnosis of disorders associated with expression of GCREC. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the

nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, Tourette's disorder, progressive supranuclear palsy, corticobasal degeneration, and familial frontotemporal dementia; a cardiovascular disorder such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, vascular tumors, complications of thrombolysis, balloon angioplasty, vascular replacement, and coronary artery bypass graft surgery, congestive heart failure, ischemic heart disease, angina pectoris, myocardial infarction, hypertensive heart disease, degenerative valvular heart disease, calcific aortic valve stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, congenital heart disease, and complications of cardiac transplantation; a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, alpha$_1$-antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hepatic tumors including nodular hyperplasias, adenomas, and carcinomas; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia,

asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a metabolic disorder such as diabetes, obesity, and osteoporosis; and an infection by a viral agent classified as adenovirus, arenavirus, bunyavirus, calicivirus, coronavirus, filovirus, hepadnavirus, herpesvirus, flavivirus, orthomyxovirus, parvovirus, papovavirus, paramyxovirus, picornavirus, poxvirus, reovirus, retrovirus, rhabdovirus, and togavirus. The polynucleotide sequences encoding GCREC may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered GCREC expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding GCREC may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding GCREC may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding GCREC in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of GCREC, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding GCREC, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified

polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding GCREC may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding GCREC, or a fragment of a polynucleotide complementary to the polynucleotide encoding GCREC, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding GCREC may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding GCREC are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary and tertiary structures of PCR products in single-stranded form, and these differences are detectable using gel electrophoresis in non-denaturing gels. In fSCCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed in silico SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual

overlapping DNA fragments which assemble into a common consensus sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of GCREC include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described below. The microarray may also be used to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the activities of therapeutic agents in the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, GCREC, fragments of GCREC, or antibodies specific for GCREC may be used as elements on a microarray. The microarray may be used to monitor or measure protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

A particular embodiment relates to the use of the polynucleotides of the present invention to generate a transcript image of a tissue or cell type. A transcript image represents the global pattern of gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by quantifying the number of expressed genes and their relative abundance under given conditions and at a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Number 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by hybridizing the polynucleotides of the present invention or their complements to the totality of transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the

hybridization takes place in high-throughput format, wherein the polynucleotides of the present invention or their complements comprise a subset of a plurality of elements on a microarray. The resultant transcript image would provide a profile of gene activity.

Transcript images may be generated using transcripts isolated from tissues, cell lines, biopsies, or other biological samples. The transcript image may thus reflect gene expression in vivo, as in the case of a tissue or biopsy sample, or in vitro, as in the case of a cell line.

Transcript images which profile the expression of the polynucleotides of the present invention may also be used in conjunction with in vitro model systems and preclinical evaluation of pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental compounds. All compounds induce characteristic gene expression patterns, frequently termed molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and toxicity (Nuwaysir, E.F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N.L. Anderson (2000) Toxicol. Lett. 112-113:467-471, expressly incorporated by reference herein). If a test compound has a signature similar to that of a compound with known toxicity, it is likely to share those toxic properties. These fingerprints or signatures are most useful and refined when they contain expression information from a large number of genes and gene families. Ideally, a genome-wide measurement of expression provides the highest quality signature. Even genes whose expression is not altered by any tested compounds are important as well, as the levels of expression of these genes are used to normalize the rest of the expression data. The normalization procedure is useful for comparison of expression data after treatment with different compounds. While the assignment of gene function to elements of a toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not necessary for the statistical matching of signatures which leads to prediction of toxicity. (See, for example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released February 29, 2000, available at http://www.niehs.nih.gov/oc/news/toxchip.htm.) Therefore, it is important and desirable in toxicological screening using toxicant signatures to include all expressed gene sequences.

In one embodiment, the toxicity of a test compound is assessed by treating a biological sample containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated biological sample are hybridized with one or more probes specific to the polynucleotides of the present invention, so that transcript levels corresponding to the polynucleotides of the present invention may be quantified. The transcript levels in the treated biological sample are compared with levels in an untreated biological sample. Differences in the transcript levels between the two samples are indicative of a toxic response caused by the test compound in the treated sample.

Another particular embodiment relates to the use of the polypeptide sequences of the present invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global

pattern of protein expression in a particular tissue or cell type. Each protein component of a proteome can be subjected individually to further analysis. Proteome expression patterns, or profiles, are analyzed by quantifying the number of expressed proteins and their relative abundance under given conditions and at a given time. A profile of a cell's proteome may thus be generated by separating and analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the separation is achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separated by isoelectric focusing in the first dimension, and then according to molecular weight by sodium dodecyl sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, supra). The proteins are visualized in the gel as discrete and uniquely positioned spots, typically by staining the gel with an agent such as Coomassie Blue or silver or fluorescent stains. The optical density of each protein spot is generally proportional to the level of the protein in the sample. The optical densities of equivalently positioned protein spots from different samples, for example, from biological samples either treated or untreated with a test compound or therapeutic agent, are compared to identify any changes in protein spot density related to the treatment. The proteins in the spots are partially sequenced using, for example, standard methods employing chemical or enzymatic cleavage followed by mass spectrometry. The identity of the protein in a spot may be determined by comparing its partial sequence, preferably of at least 5 contiguous amino acid residues, to the polypeptide sequences of the present invention. In some cases, further sequence data may be obtained for definitive protein identification.

A proteomic profile may also be generated using antibodies specific for GCREC to quantify the levels of GCREC expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lueking, A. et al. (1999) Anal. Biochem. 270:103-111; Mendoze, L.G. et al. (1999) Biotechniques 27:778-788). Detection may be performed by a variety of methods known in the art, for example, by reacting the proteins in the sample with a thiol- or amino-reactive fluorescent compound and detecting the amount of fluorescence bound at each array element.

Toxicant signatures at the proteome level are also useful for toxicological screening, and should be analyzed in parallel with toxicant signatures at the transcript level. There is a poor correlation between transcript and protein abundances for some proteins in some tissues (Anderson, N.L. and J. Seilhamer (1997) Electrophoresis 18:533-537), so proteome toxicant signatures may be useful in the analysis of compounds which do not significantly affect the transcript image, but which alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such cases.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins that are expressed in the treated biological

sample are separated so that the amount of each protein can be quantified. The amount of each protein is compared to the amount of the corresponding protein in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample. Individual proteins are identified by sequencing the amino acid residues of the individual proteins and comparing these partial sequences to the polypeptides of the present invention.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins from the biological sample are incubated with antibodies specific to the polypeptides of the present invention. The amount of protein recognized by the antibodies is quantified. The amount of protein in the treated biological sample is compared with the amount in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

In another embodiment of the invention, nucleic acid sequences encoding GCREC may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, for example, Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM)

World Wide Web site. Correlation between the location of the gene encoding GCREC on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the instant invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, GCREC, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between GCREC and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with GCREC, or fragments thereof, and washed. Bound GCREC is then detected by methods well known in the art. Purified GCREC can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding GCREC specifically compete with a test compound for binding GCREC. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with GCREC.

In additional embodiments, the nucleotide sequences which encode GCREC may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such

properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications and publications, mentioned above and below, in particular U.S. Ser. No. 60/172,852, U.S. Ser. No. 60/171,732, U.S. Ser. No. 60/176,148, and U.S. Ser. No. 60/177,331, are expressly incorporated by reference herein.

EXAMPLES

I. Construction of cDNA Libraries

Incyte cDNAs were derived from cDNA libraries described in the LIFESEQ GOLD database (Incyte Genomics, Palo Alto CA) and shown in Table 4, column 5. The Incyte cDNA shown for SEQ ID NO:40 was derived from a cDNA library constructed from bone marrow tissue. The Incyte cDNAs shown for SEQ ID NO:41 were derived from cDNA libraries constructed from small intestine, including tissues associated with Crohn's disease, from large intestine, and from brain tissues. The Incyte cDNAs shown for SEQ ID NO:42 were derived from cDNA libraries constructed from prostate tumor, small intestine, breast, and epidermal tissues. The Incyte cDNAs shown for SEQ ID NO:43 were derived cDNA libraries constructed from soft tissue tumor, fetal rib, and brain tissue associated with Huntington's disease. The Incyte cDNAs shown for SEQ ID NO:57 were derived from cDNA libraries constructed from lymphocytes and mast cells, and from breast, uterine, prostate, adrenal gland, spinal cord, tibial muscle, lung, esophagus, small intestine, and colon tissues. The Incyte cDNAs shown for SEQ ID NO:58 were derived from cDNA libraries constructed from a fallopian tube tumor, uterine endometrium, and bronchial tissue. The Incyte cDNAs shown for SEQ ID NO:59 were derived from cDNA libraries constructed from colon tissues, including cecal tumor tissue, as well as from pancreatic tumor, pituitary gland, and brain tissues. The Incyte cDNAs shown for SEQ ID NO:60 were derived from cDNA libraries constructed from brain, including brain tumor tissue and tissues associated with Huntington's disease, and from prostate tumor, cervical adenocarcinoma, breast, small intestine, and bladder tissues. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA

purity. In some cases, RNA was treated with DNase. For most libraries, poly(A)+ RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), PCDNA2.1 plasmid (Invitrogen, Carlsbad CA), or pINCY (Incyte Genomics, Palo Alto CA). Recombinant plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5α, DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids obtained as described in Example I were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows. Sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Applied Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (Applied Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VIII.

The polynucleotide sequences derived from Incyte cDNAs were validated by removing vector, linker, and poly(A) sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The Incyte cDNA sequences or translations thereof were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and hidden Markov model (HMM)-based protein family databases such as PFAM. (HMM is a probabilistic approach which analyzes consensus primary structures of gene families. See, for example, Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.) The queries were performed using programs based on BLAST, FASTA, BLIMPS, and HMMR. The Incyte cDNA sequences were assembled to produce polynucleotide sequences. Alternatively, GenBank cDNAs, GenBank ESTs, stitched sequences, stretched sequences, or Genscan-predicted coding sequences (see Examples IV and V) were used to extend Incyte cDNA assemblages to full length. Assembly was performed using programs based on Phred, Phrap, and Consed, and cDNA assemblages were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The polynucleotide sequences were translated to derive the corresponding polypeptide sequences which were subsequently analyzed by querying against databases such as the GenBank protein databases (genpept), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and hidden Markov model (HMM)-based protein family databases such as PFAM. Full length polynucleotide sequences are also analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments are generated using default parameters specified by the CLUSTAL algorithm as incorporated into the

MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

Table 7 summarizes the tools, programs, and algorithms used for the analysis and assembly of Incyte cDNA and assembled polynucleotide sequences and provides applicable descriptions, references, and threshold parameters. The first column of Table 7 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score or the lower the probability value, the greater the identity between two sequences).

The programs described above for the assembly and analysis of polynucleotide and polypeptide sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:40-78. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies are described in Table 4, column 4.

IV. Identification and Editing of Coding Sequences from Genomic DNA

Putative G-protein coupled receptors were initially identified by running the Genscan gene identification program against public genomic sequence databases (e.g., gbpri and gbhtg). Genscan is a general-purpose gene identification program which analyzes genomic DNA sequences from a variety of organisms (See Burge, C. and S. Karlin (1997) J. Mol. Biol. 268:78-94, and Burge, C. and S. Karlin (1998) Curr. Opin. Struct. Biol. 8:346-354). The program concatenates predicted exons to form an assembled cDNA sequence extending from a methionine to a stop codon. The output of Genscan is a FASTA database of polynucleotide and polypeptide sequences. The maximum range of sequence for Genscan to analyze at once was set to 30 kb. To determine which of these Genscan predicted cDNA sequences encode G-protein coupled receptors, the encoded polypeptides were analyzed by querying against PFAM models for G-protein coupled receptors (7tm_1, 7tm_2, 7tm_3, and 7tm_4). Potential G-protein coupled receptors were also identified by homology to Incyte cDNA sequences that had been annotated as G-protein coupled receptors. These selected Genscan-predicted sequences were then compared by BLAST analysis to the genpept and gbpri public databases. Where necessary, the Genscan-predicted sequences were then edited by comparison to the top BLAST hit from genpept to correct errors in the sequence predicted by Genscan, such as extra or omitted exons. BLAST analysis was also used to find any Incyte cDNA or public cDNA coverage of the Genscan-predicted sequences, thus providing evidence for transcription. When Incyte cDNA coverage was available, this information was used to correct or confirm the Genscan predicted sequence. Polynucleotide sequences, including SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:61, SEQ ID NO:62,

and SEQ ID NO:63, were obtained by assembling Genscan-predicted coding sequences with Incyte cDNA sequences and/or public cDNA sequences using the assembly process described in Example III. Alternatively, polynucleotide sequences, including SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, and SEQ ID NO:78, are full length coding regions derived entirely from edited or unedited Genscan-predicted coding sequences. Alternatively, polynucleotide sequences, including SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, and SEQ ID NO:56, are partial genes derived from the assembly and editing of Genscan-predicted sequences only.

V. Assembly of Genomic Sequence Data with cDNA Sequence Data

"Stitched" Sequences

Partial cDNA sequences were extended with exons predicted by the Genscan gene identification program described in Example IV. Partial cDNAs assembled as described in Example III were mapped to genomic DNA and parsed into clusters containing related cDNAs and Genscan exon predictions from one or more genomic sequences. Each cluster was analyzed using an algorithm based on graph theory and dynamic programming to integrate cDNA and genomic information, generating possible splice variants that were subsequently confirmed, edited, or extended to create a full length sequence. Sequence intervals in which the entire length of the interval was present on more than one sequence in the cluster were identified, and intervals thus identified were considered to be equivalent by transitivity. For example, if an interval was present on a cDNA and two genomic sequences, then all three intervals were considered to be equivalent. This process allows unrelated but consecutive genomic sequences to be brought together, bridged by cDNA sequence. Intervals thus identified were then "stitched" together by the stitching algorithm in the order that they appear along their parent sequences to generate the longest possible sequence, as well as sequence variants. Linkages between intervals which proceed along one type of parent sequence (cDNA to cDNA or genomic sequence to genomic sequence) were given preference over linkages which change parent type (cDNA to genomic sequence). The resultant stitched sequences were translated and compared by BLAST analysis to the genpept and gbpri public databases. Incorrect exons predicted by Genscan were corrected by comparison to the top BLAST hit from genpept. Sequences were further extended with additional cDNA sequences, or by inspection of genomic DNA, when necessary.

"Stretched" Sequences

Partial DNA sequences were extended to full length with an algorithm based on BLAST analysis. First, partial cDNAs assembled as described in Example III were queried against public

databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases using the BLAST program. The nearest GenBank protein homolog was then compared by BLAST analysis to either Incyte cDNA sequences or GenScan exon predicted sequences described in Example IV. A chimeric protein was generated by using the resultant high-scoring segment pairs (HSPs) to map the translated sequences onto the GenBank protein homolog. Insertions or deletions may occur in the chimeric protein with respect to the original GenBank protein homolog. The GenBank protein homolog, the chimeric protein, or both were used as probes to search for homologous genomic sequences from the public human genome databases. Partial DNA sequences were therefore "stretched" or extended by the addition of homologous genomic sequences. The resultant stretched sequences were examined to determine whether it contained a complete gene.

VI. Chromosomal Mapping of GCREC Encoding Polynucleotides

The sequences which were used to assemble SEQ ID NO:40-78 were compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:40-78 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 7). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO:, to that map location.

Map locations are represented by ranges, or intervals, or human chromosomes. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site (http://www.ncbi.nlm.nih.gov/genemap/), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

VII. Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel (1995) supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score x Percent Identity}}{5 \times \text{minimum } \{\text{length(Seq. 1)}, \text{length(Seq. 2)}\}}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

Alternatively, polynucleotide sequences encoding GCREC are analyzed with respect to the tissue sources from which they were derived. For example, some full length sequences are assembled, at least in part, with overlapping Incyte cDNA sequences (see Example III). Each cDNA sequence is derived from a cDNA library constructed from a human tissue. Each human tissue is classified into one of the following organ/tissue categories: cardiovascular system; connective tissue; digestive system; embryonic structures; endocrine system; exocrine glands; genitalia, female; genitalia, male; germ cells; hemic and immune system; liver; musculoskeletal system; nervous system; pancreas; respiratory system; sense organs; skin; stomatognathic system; unclassified/mixed; or urinary tract. The number of libraries in each category is counted and divided by the total number of libraries across all categories. Similarly, each human tissue is classified into one of the following disease/condition categories: cancer, cell line, developmental, inflammation, neurological, trauma, cardiovascular, pooled, and other, and the number of libraries in each category is counted and divided by the total number of libraries across all categories. The resulting percentages reflect the tissue- and disease-specific expression of cDNA encoding GCREC. cDNA sequences and cDNA library/tissue information are found in the LIFESEQ

GOLD database (Incyte Genomics, Palo Alto CA).

VIII. Extension of GCREC Encoding Polynucleotides

Full length polynucleotide sequences were also produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer was synthesized to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+}, $(NH_4)_2SO_4$, and 2-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 µl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 µl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 µl to 10 µl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were

religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems).

In like manner, full length polynucleotide sequences are verified using the above procedure or are used to obtain 5' regulatory sequences using the above procedure along with oligonucleotides designed for such extension, and an appropriate genomic library.

IX. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:40-78 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μCi of [γ-^{32}P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and

compared.

X. Microarrays

The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, supra.), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Schena (1999), supra). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645; Marshall, A. and J. Hodgson (1998) Nat. Biotechnol. 16:27-31.)

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser desorbtion and mass spectrometry may be used for detection of hybridization. The degree of complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is described in detail below.

Tissue or Cell Sample Preparation

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and poly(A)$^+$ RNA is purified using the oligo-(dT) cellulose method. Each poly(A)$^+$ RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/μl oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/μl RNase inhibitor, 500 μM dATP, 500 μM dGTP, 500 μM dTTP, 40 μM dCTP, 40 μM dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)$^+$ RNA with GEMBRIGHT kits (Incyte). Specific control poly(A)$^+$ RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA. After incubation at 37°C for 2 hr, each reaction sample (one with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85°C to the stop the reaction and degrade the RNA. Samples are purified

using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14 µl 5X SSC/0.2% SDS.

Microarray Preparation

Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 µg. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5,807,522 , incorporated herein by reference. 1 µl of the array element DNA, at an average concentration of 100 ng/µl, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60° C followed by washes in 0.2% SDS and distilled water as before.

Hybridization

Hybridization reactions contain 9 µl of sample mixture consisting of 0.2 µg each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65° C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm^2 coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140 µl of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60° C. The arrays are washed for 10 min at 45° C in a first wash buffer (1X SSC,

0.1% SDS), three times for 10 minutes each at 45°C in a second wash buffer (0.1X SSC), and dried.

Detection

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477, Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital (A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

XI. Complementary Polynucleotides

Sequences complementary to the GCREC-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring GCREC. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of GCREC. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the GCREC-encoding transcript.

XII. Expression of GCREC

Expression and purification of GCREC is achieved using bacterial or virus-based expression systems. For expression of GCREC in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express GCREC upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of GCREC in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding GCREC by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, GCREC is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from GCREC at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification

using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified GCREC obtained by these methods can be used directly in the assays shown in Examples XVI, XVII, and XVIII, where applicable.

XIII. Functional Assays

GCREC function is assessed by expressing the sequences encoding GCREC at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include PCMV SPORT (Life Technologies) and PCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of GCREC on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding GCREC and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding GCREC and other genes of interest can be analyzed by northern analysis or

microarray techniques.

XIV. Production of GCREC Specific Antibodies

GCREC substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the GCREC amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Applied Biosystems) using FMOC chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-GCREC activity by, for example, binding the peptide or GCREC to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XV. Purification of Naturally Occurring GCREC Using Specific Antibodies

Naturally occurring or recombinant GCREC is substantially purified by immunoaffinity chromatography using antibodies specific for GCREC. An immunoaffinity column is constructed by covalently coupling anti-GCREC antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing GCREC are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of GCREC (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/GCREC binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and GCREC is collected.

XVI. Identification of Molecules Which Interact with GCREC

Molecules which interact with GCREC may include agonists and antagonists, as well as molecules involved in signal transduction, such as G proteins. GCREC, or a fragment thereof, is labeled with ^{125}I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) A fragment of GCREC includes, for example, a fragment comprising one or more of the three extracellular loops, the extracellular N-terminal region, or the third intracellular loop. Candidate

molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled GCREC, washed, and any wells with labeled GCREC complex are assayed. Data obtained using different concentrations of GCREC are used to calculate values for the number, affinity, and association of GCREC with the candidate ligand molecules.

Alternatively, molecules interacting with GCREC are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989) Nature 340:245-246, or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech). GCREC may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

Potential GCREC agonists or antagonists may be tested for activation or inhibition of GCREC receptor activity using the assays described in sections XVII and XVIII. Candidate molecules may be selected from known GPCR agonists or antagonists, peptide libraries, or combinatorial chemical libraries.

Methods for detecting interactions of GCREC with intracellular signal transduction molecules such as G proteins are based on the premise that internal segments or cytoplasmic domains from an orphan G protein-coupled seven transmembrane receptor may be exchanged with the analogous domains of a known G protein-coupled seven transmembrane receptor and used to identify the G-proteins and downstream signaling pathways activated by the orphan receptor domains (Kobilka, B.K. et al. (1988) Science 240:1310-1316). In an analogous fashion, domains of the orphan receptor may be cloned as a portion of a fusion protein and used in binding assays to demonstrate interactions with specific G proteins. Studies have shown that the third intracellular loop of G protein-coupled seven transmembrane receptors is important for G protein interaction and signal transduction (Conklin, B.R. et al. (1993) Cell 73:631-641). For example, the DNA fragment corresponding to the third intracellular loop of GCREC may be amplified by the polymerase chain reaction (PCR) and subcloned into a fusion vector such as pGEX (Pharmacia Biotech). The construct is transformed into

saline. Bound G subunits are detected by [^{32}P]ADP-ribosylation with pertussis or cholera toxins. The reactions are terminated by the addition of SDS sample buffer (4.6% (w/v) SDS, 10% (v/v) β-mercaptoethanol, 20% (w/v) glycerol, 95.2 mM Tris-HCl, pH 6.8, 0.01% (w/v) bromphenol blue). The [^{32}P]ADP-labeled proteins are separated on 10% SDS-PAGE gels, and autoradiographed. These gels are transferred to nitrocellulose paper, blocked with blotto (5% nonfat dried milk, 50 mM Tris-HCl (pH 8.0), 2 mM $CaCl_2$, 80 mM NaCl, 0.02% NaN_3, and 0.2% Nonidet P-40) for 1 hour at room temperature, followed by incubation for 1.5 hours with Gα subtype selective antibodies (1:500; Calbiochem-Novabiochem). After three washes, blots are incubated with horseradish peroxidase (HRP)-conjugated goat anti-rabbit immunoglobulin (1:2000, Cappel, Westchester PA) and visualized by the chemiluminescence-based ECL method (Amersham Corp.).

XVII. Demonstration of GCREC Activity

An assay for GCREC activity measures the expression of GCREC on the cell surface. cDNA encoding GCREC is transfected into an appropriate mammalian cell line. Cell surface proteins are labeled with biotin as described (de la Fuente, M.A. et al. (1997) Blood 90:2398-2405). Immunoprecipitations are performed using GCREC-specific antibodies, and immunoprecipitated samples are analyzed using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting techniques. The ratio of labeled immunoprecipitant to unlabeled immunoprecipitant is proportional to the amount of GCREC expressed on the cell surface.

In the alternative, an assay for GCREC activity is based on a prototypical assay for ligand/receptor-mediated modulation of cell proliferation. This assay measures the rate of DNA synthesis in Swiss mouse 3T3 cells. A plasmid containing polynucleotides encoding GCREC is added to quiescent 3T3 cultured cells using transfection methods well known in the art. The transiently transfected cells are then incubated in the presence of [^{3}H]thymidine, a radioactive DNA precursor molecule. Varying amounts of GCREC ligand are then added to the cultured cells. Incorporation of [^{3}H]thymidine into acid-precipitable DNA is measured over an appropriate time interval using a radioisotope counter, and the amount incorporated is directly proportional to the amount of newly synthesized DNA. A linear dose-response curve over at least a hundred-fold GCREC ligand concentration range is indicative of receptor activity. One unit of activity per milliliter is defined as the concentration of GCREC producing a 50% response level, where 100% represents maximal incorporation of [^{3}H]thymidine into acid-precipitable DNA (McKay, I. and I. Leigh, eds. (1993) Growth Factors: A Practical Approach, Oxford University Press, New York NY, p. 73.)

In a further alternative, the assay for GCREC activity is based upon the ability of GPCR family proteins to modulate G protein-activated second messenger signal transduction pathways (e.g., cAMP; Gaudin, P. et al. (1998) J. Biol. Chem. 273:4990-4996). A plasmid encoding GCREC is transfected into a mammalian cell line (e.g., Chinese hamster ovary (CHO) or human embryonic

kidney (HEK-293) cell lines) using methods well-known in the art. Transfected cells are grown in 12-well trays in culture medium for 48 hours, then the culture medium is discarded, and the attached cells are gently washed with PBS. The cells are then incubated in culture medium with or without ligand for 30 minutes, then the medium is removed and cells lysed by treatment with 1 M perchloric acid. The cAMP levels in the lysate are measured by radioimmunoassay using methods well-known in the art. Changes in the levels of cAMP in the lysate from cells exposed to ligand compared to those without ligand are proportional to the amount of GCREC present in the transfected cells.

To measure changes in inositol phosphate levels, the cells are grown in 24-well plates containing $1x10^5$ cells/well and incubated with inositol-free media and [^{3}H]myoinositol, 2 μCi/well, for 48 hr. The culture medium is removed, and the cells washed with buffer containing 10 mM LiCl followed by addition of ligand. The reaction is stopped by addition of perchloric acid. Inositol phosphates are extracted and separated on Dowex AG1-X8 (Bio-Rad) anion exchange resin, and the total labeled inositol phosphates counted by liquid scintillation. Changes in the levels of labeled inositol phosphate from cells exposed to ligand compared to those without ligand are proportional to the amount of GCREC present in the transfected cells.

XVIII. Identification of GCREC Ligands

GCREC is expressed in a eukaryotic cell line such as CHO (Chinese Hamster Ovary) or HEK (Human Embryonic Kidney) 293 which have a good history of GPCR expression and which contain a wide range of G-proteins allowing for functional coupling of the expressed GCREC to downstream effectors. The transformed cells are assayed for activation of the expressed receptors in the presence of candidate ligands. Activity is measured by changes in intracellular second messengers, such as cyclic AMP or Ca^{2+}. These may be measured directly using standard methods well known in the art, or by the use of reporter gene assays in which a luminescent protein (e.g. firefly luciferase or green fluorescent protein) is under the transcriptional control of a promoter responsive to the stimulation of protein kinase C by the activated receptor (Milligan, G. et al. (1996) Trends Pharmacol. Sci. 17:235-237). Assay technologies are available for both of these second messenger systems to allow high throughput readout in multi-well plate format, such as the adenylyl cyclase activation FlashPlate Assay (NEN Life Sciences Products), or fluorescent Ca^{2+} indicators such as Fluo-4 AM (Molecular Probes) in combination with the FLIPR fluorimetric plate reading system (Molecular Devices). In cases where the physiologically relevant second messenger pathway is not known, GCREC may be coexpressed with the G-proteins $G_{\alpha 15/16}$ which have been demonstrated to couple to a wide range of G-proteins (Offermanns, S. and M.I. Simon (1995) J. Biol. Chem. 270:15175-15180), in order to funnel the signal transduction of the GCREC through a pathway involving phospholipase C and Ca^{2+} mobilization. Alternatively, GCREC may be expressed in engineered yeast systems which lack endogenous GPCRs, thus providing the advantage of a null background for GCREC activation screening. These yeast systems substitute a

human GPCR and Ga protein for the corresponding components of the endogenous yeast pheromone receptor pathway. Downstream signaling pathways are also modified so that the normal yeast response to the signal is converted to positive growth on selective media or to reporter gene expression (Broach, J.R. and J. Thorner (1996) Nature 384 (supp.):14-16). The receptors are screened against putative ligands including known GPCR ligands and other naturally occurring bioactive molecules. Biological extracts from tissues, biological fluids and cell supernatants are also screened.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Incyte Project ID	Polypeptide SEQ ID NO:	Incyte Polypeptide ID	Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID
104941	1	104941CD1	40	104941CB1
1499408	2	1499408CD1	41	1499408CB1
3168839	3	3168839CD1	42	3168839CB1
3291235	4	3291235CD1	43	3291235CB1
7472001	5	7472001CD1	44	7472001CB1
7472003	6	7472003CD1	45	7472003CB1
7472004	7	7472004CD1	46	7472004CB1
7475687	8	7475687CP1	47	7475687CT1
7483029	9	7483029CP1	48	7483029CT1
7477933	10	7477933CP1	49	7477933CT1
7475164	11	7475164CP1	50	7475164CT1
7473909	12	7473909CP1	51	7473909CT1
7475252	13	7475252CP1	52	7475252CT1
7927572	14	7927572CP1	53	7927572CT1
7481257	15	7481257CP1	54	7481257CT1
7485790	16	7485790CP1	55	7485790CT1
7482993	17	7482993CP1	56	7482993CT1
2829053	18	2829053CD1	57	2829053CB1
3068234	19	3068234CD1	58	3068234CB1
5029478	20	5029478CD1	59	5029478CB1
5102576	21	5102576CD1	60	5102576CB1
2200534	22	2200534CD1	61	2200534CB1
3275821	23	3275821CD1	62	3275821CB1
3744167	24	3744167CD1	63	3744167CB1
7472007	25	7472007CD1	64	7472007CB1
7472008	26	7472008CD1	65	7472008CB1
7472013	27	7472013CD1	66	7472013CB1
7472015	28	7472015CD1	67	7472015CB1
7472016	29	7472016CD1	68	7472016CB1

Table 1 (cont.)

Incyte Project ID	Polypeptide SEQ ID NO:	Incyte Polypeptide ID	Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID
7472017	30	7472017CD1	69	7472017CB1
7472018	31	7472018CD1	70	7472018CB1
7472019	32	7472019CD1	71	7472019CB1
7472021	33	7472021CD1	72	7472021CB1
7472009	34	7472009CD1	73	7472009CB1
7472010	35	7472010CD1	74	7472010CB1
7472011	36	7472011CD1	75	7472011CB1
7472012	37	7472012CD1	76	7472012CB1
7472014	38	7472014CD1	77	7472014CB1
7472020	39	7472020CD1	78	7472020CB1

Table 2

Polypeptide SEQ ID NO:	Incyte Polypeptide ID	GenBank ID NO:	Probability Score	GenBank Homolog
1	104941CD1	g7211316	6.9E-146	Olfactory receptor [Callithrix jacchus]
2	1499408CD1	g202806	5.20E-162	Vasopressin receptor [Rattus norvegicus]
3	3168839CD1	g3618229	2.2E-44	G protein-linked P2Y4 receptor [Rattus norvegicus]
4	3291235CD1	g3287369	1.40E-126	A-2 [Mus musculus]
5	7472001CD1	g1256393	2.20E-122	Taste bud receptor protein TB 641 [Rattus norvegicus]
6	7472003CD1	g4378765	1.20E-169	Orphan G protein-coupled receptor GPR54 [Rattus norvegicus]
7	7472004CD1	g1698952	6.30E-118	High-affinity lysophosphatidic acid receptor [Xenopus laevis]
8	7475687CP1	g1256393	4.70E-90	Taste bud receptor protein TB 641 [Rattus norvegicus]
9	7483029CP1	g2447219	2.50E-75	OLF4 [Homo sapiens]
10	7477933CP1	g2792016	4.90E-79	Olfactory receptor [Homo sapiens]
11	7475164CP1	g517366	3.00E-111	Olfactory receptor [Rattus norvegicus]
12	7473909CP1	g4680264	1.90E-22	Odorant receptor S25 [Mus musculus]
13	7475252CP1	g2447219	6.50E-61	OLF4 [Homo sapiens]
14	7927572CP1	g8100089	6.7E-54	Putative taste receptor HTR2 [Homo sapiens]
15	7481257CP1	g4826521	4.00E-29	dJ88J8.1 (novel 7 transmembrane receptor (rhodopsin family) (olfactory receptor like protein (hs6M1-15)) [Homo sapiens]
16	7485790CP1	g2447219	3.00E-40	OLF4 [Homo sapiens]
17	7482993CP1	g1314665	3.10E-54	CfOLF3 [Canis familiaris]
18	2829053CD1			
19	3068234CD1	g5922725	3.1E-190	Lysophosphatidic acid G protein-coupled receptor [Homo sapiens]
20	5029478CD1	g1049072	3.6E-21	Galanin receptor GALR1 [Rattus norvegicus] (Cloning and characterization of the rat GALR1 galanin receptor from Rin14B insulinoma cells. Brain Res. Mol. Brain Res. 1995 Dec 28;34(2):179-189.)

Table 2 (cont.)

Polypeptide SEQ ID NO:	Incyte Polypeptide ID	GenBank ID NO:	Probability Score	GenBank Homolog
21	5102576CD1	g2792016	2.4E-92	Olfactory receptor [Homo sapiens] (Molecular cloning and chromosomal mapping of olfactory receptor genes expressed in the male germ line: evidence for their wide distribution in the human genome. Biochem. Biophys. Res. Commun. 1997 Aug 18;237(2):283-287.)
22	2200534CD1	g5051404	4.6e-131	573K1.15 (mm17M1-6) 7-transmembrane olfactory receptor-like protein (rhodopsin family) [Mus musculus]
23	3275821CD1	g182742	1.5e-29	Formyl peptide receptor [Homo sapiens] (Murphy, P.M. et al. (1992) J. Biol. Chem. 267:7637-7643)
24	3744167CD1	g9186902	1.2E-240	Leukotriene B4 receptor, BLT2 [Mus musculus]
25	7472007CD1	g7638409	1.3E-199	Olfactory receptor P2 [Mus musculus]
26	7472008CD1	g4218182	1.0e-89	dJ271M21.2 (hs6M1-12 (7 transmembrane receptor (rhodopsin family) (olfactory receptor like) protein)) [Homo sapiens]
27	7472013CD1	g205846	2.5e-70	Olfactory protein [Rattus norvegicus]
28	7472015CD1	g1204095	2.5e-25	Dopamine receptor [Fugu rubripes]
29	7472016CD1	g6090796	1.1E-215	Olfactory receptor [Gorilla gorilla]
30	7472017CD1	g3757727	2.0e-61	dJ80I19.7 (olfactory receptor-like protein (hs6M1-3)) [Homo sapiens]
31	7472018CD1	g6644328	2.3E-112	Orphan G protein-coupled receptor GPR26 [Rattus norvegicus]
32	7472019CD1	g5869916	2.7e-73	Olfactory receptor [Mus musculus]
33	7472021CD1	g6090804	2.6E-94	Olfactory receptor [Gorilla gorilla]
34	7472009CD1	g1016362	1.6e-68	OL1 receptor [Rattus norvegicus]
35	7472010CD1	g2317704	7.3e-80	Olfactory receptor [Rattus norvegicus]
36	7472011CD1	g6178008	4.9E-114	Odorant receptor MOR18 [Mus musculus]
37	7472012CD1	g205816	6.8e-84	Olfactory protein [Rattus norvegicus]
38	7472014CD1	g205816	3.9e-88	Olfactory protein [Rattus norvegicus]
39	7472020CD1	g2792016	1.9e-97	Olfactory receptor [Homo sapiens]

Table 3

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
1	104941CD1	311	S68 S189 S292 Y310	N5 N66	7 transmembrane receptor (rhodopsin family): G42-Y291 GPCR signature: K91-P130, I208-Y219, Y283-K299, Y103-S151 Olfactory receptor signature: M60-K81, F178-D192, F239-G254, A275-L286, S292-Q306	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfileScan
					Transmembrane domains: I31-I47, P211-I229	HMMER
2	1499408CD1	891	T148 S686 S114 S248 S350 S481 S501 T628 T814 S856 T84 S140 T144 T325 T411 T543 S568 S676 T706 T788 Y372	N378	ATP/GTP binding site (P-loop): G202-T209	MOTIFS
3	3168839CD1	422	T232 S178 T342 S363 S371 S397 T21 S211 S226 T307 S332 S367	N4 N9 N251 N323	7 transmembrane receptor (rhodopsin family): L39-Y297 Rhodopsin-like GPCR superfamily: L24-L48, V57-R78, F101-I123, V137-R158, V192-F215, T232-V256, L279-R305	MOTIFS HMMER-PFAM BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS
					Transmembrane domains: V275-L295	HMMER
4	3291235CD1	609	S228 S229 S396 S456 S324 S328 S364 S417 S466 T506 S568 S590 S153 S268 T392 S462 S482 S560 Y348		7 transmembrane receptor (rhodopsin family): E80-E154 GPCR signatures: F76-P115, F395-A405,, A442-E458, E509-P526	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
					Transmembrane domain: V174-L199	HMMER

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
5	7472001CD1	313	S68 T194 T200 S267 T309 T138 T164 T290 S306	N5 N85	7 transmembrane receptor (rhodopsin family): G41-I259 GPCR signature: K91-P130, T281-K297, Y103-A147 Olfactory receptor signature: M60-R81, F178-D192, F239-V254, A273-L284, T290-L304	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfileScan
					Signal peptide: M1-T38	HMMER SPScan
					Transmembrane domains: F30-T48, F63-M83	HMMER
6	7472003CD1	398	S36 T155	N10 N18 N28	7 transmembrane receptor (rhodopsin family): G59-Y323 GPCR signature: W108-P147, Y213-Y224, A256-F282, N315-R331, N119-I166 Neuropeptide Y receptor signature: R69-I81, L321-F334	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfileScan
					Transmembrane domain: A42-Y65	HMMER
7	7472004CD1	369	S228 T94 T218 S339 T350	N12	7 transmembrane receptor (rhodopsin family): G48-Y321 Rhodopsin-like GPCR signature: T33-Y57, I66-F87, F111-I133, R144-V165, V193-L216, A262-V286, S303-H329	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
					Transmembrane domains: T33-V51, M109-I125, Y189-M213, M256-V275	HMMER
8	7475687CP1	194	T186 T76 T82 T46 T172		7 transmembrane receptor (rhodopsin family): M1-Y171 Opsins retinal binding site: Y142-N194 Olfactory receptor signature: F60-D74, F121-V136, A155-L166, T172-T186	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfileScan

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databas s
9	7483029CP1	173	T16 S34 T60	N32 N167	7 transmembrane receptor (rhodopsin family): G8-C146 Rhodopsin-like GPCR signature: M26-K47, F71-I93, L107-I128	MOTIFS HMMER-PFAM BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS
					Signal peptide: M1-L22	SPScan HMMER
					Transmembrane domains: M68-A86, M103-L121	HMMER
10	7477933CP1	220	S172		7 transmembrane receptor (rhodopsin family): P1-C192 Olfactory receptor signature: M2-K23, F120-D134, F181-G196 Rhodopsin-like GPCR signature: L47-I69, I142-V165	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
					Transmembrane domains: M44-A62, V85-T110	HMMER
11	7475164CP1	302	T296 S58 S84 T107 T257 T9 T69 S128 T151 S282		7 transmembrane receptor (rhodopsin family): G32-I193 GPCR signature: N81-P120, I273-K289, S93-L142 Olfactory receptor signature: V50-K71, Y168-S182, F229-G244, S265-L276, S282-T296	MOTIFS HMMER-PFAM BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS
					Transmembrane domains: F19-L39, I188-I207	HMMER
12	7473909CP1	110	S70 S36 T66 S94		GPCR signature: I85-K101 Olfactory receptor signature: F41-G56, A77-L88, S94-Y108	MOTIFS BLIMPS-BLOCKS BLIMPS-PRINTS

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
13	7475252CP1	178	S66 S151 S136	N4 N64	7 transmembrane receptor (rhodopsin family): G40-L153 Rhodopsin-like GPCR signature: V25-S49, M58-K79, L103-I125, S102-S151	MOTIFS HMMER-PFAM BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS
					Transmembrane domains: L29-I45, M100-M117	HMMER
14	7927572CP1	92			Olfactory receptor signature: F25-D39	MOTIFS BLIMPS-PRINTS
15	7481257CP1	97			7 transmembrane receptor (rhodopsin family): M1-Y96 GPCR signature: V13-Y24, Q41-Q67 Olfactory receptor signature: F44-G59, L80-L91	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
					Signal peptide: M1-G27	SPScan HMMER
					Transmembrane domain: M8-Y24	HMMER
16	7485790CP1	133	S74		7 transmembrane receptor (rhodopsin family): R22-V128 GPCR signature: G71-P110	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
					Transmembrane domain: M82-A100	HMMER
17	7482993CP1	213	S85 S205 S159 T183	N83	7 transmembrane receptor (rhodopsin family): S2-Y182 GPCR signature: R127-R153, S2-A38 Olfactory receptor signature: F69-N83, F130-G145, V166-L177, T183-G197	MOTIFS HMMER-PFAM BLIMPS-BLOCKS ProfileScan BLIMPS-PRINTS
					Transmembrane domains: P102-I120, F130-V152	HMMER

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
18	2829053CD1	180	S30 S41 S109 S125 S140 S35 S36 S149		Beta-1 adrenergic receptor signature: I148-S166	MOTIFS BLIMPS-PRINTS
					Signal peptide: M1-S67	SPScan
19	3068234CD1	353	T146 T217 T233 S321 S17 T21 S294 S329 T141 S229 T303 Y14	N15 N139 N172 N349	7 transmembrane receptor (rhodopsin family): S47-Y293 Rhodopsin-like GPCR superfamily signature: I32-I56, F65-L86, L109-I131, R144-L165, Y187-Y210, L237-L261, K275-Y301	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
					Transmembrane domains: V36-I56, T146-G166, Y187-L207, T240-V258	HMMER
20	5029478CD1	361	T242 S256 S237 S350	N21 N322	7 transmembrane receptor (rhodopsin family): G57-Y321 Rhodopsin-like GPCR superfamily signature: V42-A66, T74-V95, M118-I140, A154-V175, D208-L231, L262-L286, F303-E329	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
					Transmembrane domains: T45-V65, V124-Q144, V209-I233, L266-N291	HMMER
21	5102576CD1	251	S119 S196		7 transmembrane receptor (rhodopsin family): R8-C251 GPCR signature: R57-P96 Olfactory receptor signature: M26-K47, L144-D158, F205-G220, A241-C252	MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS
					Transmembrane domains: T66-D88, V109-T134	HMMER

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
22	2200534CD1	315	S6 S136 T291	N4 N154	G-protein coupled receptor: DM00013(P232750)17-306: S17-L305 DM00013(A570690)15-304: F16-L305 DM00013(P47881)20-309: P20-L305 PD149621: T246-L305 PD000921: C168-L245 PD002495: N4-L47 BL00237: L89-P128, L207-Y218, T282-K298 Olfactory receptor PR00245: M58-P79, F176-G190, V238-G253, V274-L285, T291-L305	HMMER BLIMPS-PRINTS BLIMPS-BLOCKS HMMER-PFAM MOTIFS
					G-protein coupled receptors	BLAST-PRODOM BLAST-DOMO
					Transmembrane domains: V204-M228, G40-Y290	HMMER
23	3275821CD1	470	T3 T18 T326 T332 T340 S350 S424 S451 T459 S192	N47	G-protein coupled receptor: DM00013(P21462)20-317: V34-L306 PD000009: L68-F169 BL00237: W97-P136, G201-H212, A230-A256, N287-R303 GPCR profile: F109-V155 Rhodopsin GPCR family PR00237: W31-G55, L66-Q87, W111-A133, L147-V168, L193-Q216, F235-L259, L277-R303	HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfileScan MOTIFS
					G-protein coupled receptors	BLAST-PRODOM BLAST-DOMO
					Transmembrane domains: T33-A51, L68-L259	HMMER

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
24	3744167CD1	358	T291 S15 T18 S215	N10 N38 N342	G-protein coupled receptor: DM00013(P46092)27-318: S19-F290 DM00013(P31391)41-326: L29-L304 DM00013|P35414|22-324: W16-F290 BL00237: W87-P126, F190-Y201, R217-V243, S280-L296 GPCR profile: Y99-V145 Rhodopsin GPCR family PR00237: T22-A46, A57-F78, C101-V123, L137-V158, L182-L205, V222-L246, R270-L296	HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS ProfileScan MOTIFS
					G-protein coupled receptors	BLAST-PRODOM BLAST-DOMO
					Transmembrane domains: A138-Y159, G37-Y288	HMMER

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
25	7472007CD1	314	S270 S291 S311 T49 S67 S193	N4 N65	Signal peptide: M1-Q56	SPScan
					Transmembrane domains: L29-V48, L208-M228	HMMER
					7 transmembrane receptor (rhodopsin family) signature: G41-Y290	HMMER-PFAM
					G-protein coupled receptor signatures: T90-P129, I207-Y218, T282-K298	BLIMPS-BLOCKS
					G-protein coupled receptor signature: Y102-A147	ProfileScan
					G-protein coupled receptor signature: A110-A125	MOTIFS
					Olfactory receptor signatures: M59-K80, F177-D191, F238-S253, I274-L285, S291-I305	BLIMPS-PRINTS
					Melanocortin receptor family: A5-L63	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily: L26-I50, M59-K80, F104-I126, F153-V174, A199-L222, A237-R261, K272-K298	BLIMPS-PRINTS
					G-protein coupled receptor: DM00013|P23270|18-311: L23-H306	BLAST-DOMO
					G-protein coupled receptor DM00013|P23267|20-309: L27-I305	BLAST-DOMO
					G-protein coupled receptor DM00013|P23275|17-306: L23-I305	BLAST-DOMO
					G-protein coupled receptor DM00013|P30953|18-306: L19-H306	BLAST-DOMO
					Olfactory receptor PD000921: F168-L246	BLAST-PRODOM
					Olfactory receptor PD149621: V247-R307	BLAST-PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
26	7472008CD1	365	S78 T192 S199 T320 S343 S47 S66 S78 S96 S217 T222 T337 T361	N94	Transmembrane domain: I226-L244	HMMER
					7 transmembrane receptor (rhodopsin family) signature: G70-Y319	HMMER-PFAM
					G-protein coupled receptor signatures: K119-P158, L236-S247, K264-Q290, T311-H327	BLIMPS-BLOCKS
					Olfactory receptor signatures: M88-Q109, V206-D220, F267-G282, L303-L314, T320-K334	BLIMPS-PRINTS
					Melanocortin receptor family: V73-L84, K80-L92	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily: L55-L79, M88-Q109, F133-V155, M228-A251, A266-Q290, K301-H327	BLIMPS-PRINTS
					Olfactory receptor PD000921: L195-L275	BLAST-PRODOM
					Olfactory receptor PD149621: V276-K331	BLAST-PRODOM
					G-protein coupled receptor: DM00013|P30955|18-305: L61-L326	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23269|15-304: L61-L326	BLAST-DOMO
					G-protein coupled receptor DM00013|A57069|15-304: D59-L326	BLAST-DOMO
					G-protein coupled receptor DM00013|P23275|17-306: T67-L326	BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
27	7472013CD1	317	S68 S193	N6 N22 N43	Signal peptide: M1-G42	SPScan
					Transmembrane domain: I23-L41	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: G42-L155, A279-Y295	HMMER-PFAM
					G-protein coupled receptor signatures: P91-P130, M212-Y223, T287-K303	BLIMPS-BLOCKS
					G-protein coupled receptor signature: F103-L148	ProfileScan
					G-protein coupled receptor signature: T111-A126	MOTIFS
					Olfactory receptor signatures: M60-Q81, F182-D196, V243-G258, A279-A290, S296-L310	BLIMPS-PRINTS
					Melanocortin receptor family: W52-L64	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily: L27-S51, M60-Q81, F105-I127, R141-G162, I204-G227, A242-Q266, M277-K303	BLIMPS-PRINTS
					GPR3 orphan receptor signature: V161-N178	BLIMPS-PRINTS
					G-protein coupled receptor: DM00013|P23274|18-306: L27-L310	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23272|18-306: Y25-L310	BLAST-DOMO
					G-protein coupled receptor: DM00013|P30953|18-306: L27-L310	BLAST-DOMO
					G-protein coupled receptor: DM00013|P30955|18-305: L27-L310	BLAST-DOMO
					Olfactory receptor PD000921: G174-L250	BLAST-PRODOM
					Olfactory receptor PD149621: T251-L310	BLAST-PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
28	7472015CD1	335	T73 S79 S214 S309 T217 S329 S331		Signal peptide: M1-A20	HMMER
					Signal peptide: M1-A20	SPScan
					Transmembrane domains: F5-V27, L45-T63, M117-I136	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: T21-Y279	HMMER-PFAM
					G-protein coupled receptor signatures: R71-P110, F174-Y185, P218-T244, N271-R287	BLIMPS-BLOCKS
					G-protein coupled receptor signature: F84-L129	ProfileScan
					G-protein coupled receptor signature: A91-I106	MOTIFS
					Rhodopsin-like GPCR superfamily: S6-L30, S40-L61, V85-I107, V121-G142, V166-L189, A223-V247, E261-R287	BLIMPS-PRINTS
					G-protein coupled receptor: DM00013|P41596|137-461: G8-D220	BLAST-DOMO
					G-protein coupled receptor: DM00013|P47800|29-338: G8-Y281	BLAST-DOMO
					G-protein coupled receptor: DM00013|P31388|20-336: G8-P218	BLAST-DOMO
					G-protein coupled receptor: DM00013|JN0591|20-336: G8-P218	BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
29	7472016CD1	309	S8 S67 S188 S266 S137 S229 S266 S289	N5 N65 N264	Signal peptide: M1-L55	SPScan
					Transmembrane domains: Y28-A48, M199-I218	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: G41-Y288	HMMER-PFAM
					G-protein coupled receptor signatures: K90-P129, F206-Y217, L234-R260, T280-K296	BLIMPS-BLOCKS
					G-protein coupled receptor signature: Y102-A146	ProfileScan
					Olfactory receptor signatures: M59-K80, F177-D191, F237-G252, I272-L283, S289-F303	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily: F26-C50, M59-K80, M104-I126 S140-L161, M198-F219, A270-K296	BLIMPS-PRINTS
					G-protein coupled receptor: DM00013|P23266|17-306: Q20-L302	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23274|18-306: E22-L299	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23269|15-304: Q21-L299	BLAST-DOMO
					G-protein coupled receptor: DM00013|P30955|18-305: E22-L302	BLAST-DOMO
					Olfactory receptor PD149621: T245-S309	BLAST-PRODOM
					Olfactory receptor PD000921: L166-L244	BLAST-PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
30	7472017CD1	236	S7 T217	N5 N189	Signal peptide: M1-G42	SPScan
					Transmembrane domains: C31-M52, V123-L141	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: F12-Y216	HMMER-PFAM
					G-protein coupled receptor signatures: K24-P63, L133-Y144, C161-Q187, T208-K224	BLIMPS-BLOCKS
					G-protein coupled receptor signature: Y36-V81	ProfileScan
					G-protein coupled receptor signature: T44-A59	MOTIFS
					Olfactory receptor signatures: L164-G179, I200-L211, T217-N231	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily: S38-V60, L125-A148, G163-Q187, K198-K224	BLIMPS-PRINTS
					Olfactory receptor PD149621: V173-T236	BLAST-PRODOM
					Olfactory receptor PD000921: C103-I172	BLAST-PRODOM
					G-protein coupled receptor: DM00013|P23269|15-304: L15-L227	BLAST-DOMO
					G-protein coupled receptor: DM00013|P30953|18-306: L15-L227	BLAST-DOMO
					G-protein coupled receptor: DM00013|A57069|15-304: L15-R228	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23275|17-306: M1-L227	BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
31	7472018CD1	363	Y294 S321 S325 T353 S157 T210 S223 T240 T316 T340	N47 N348 N355	Signal peptide: M1-A24	HMMER
					Signal peptide: M1-A24	SPScan
					7 transmembrane receptor (rhodopsin family) signatures: S22-Y294	HMMER-PFAM
					G-protein coupled receptor signatures: T72-P111, F181-S192, R234-T260, K286-R302	BLIMPS-BLOCKS
					Rhodopsin-like GPCR superfamily: L7-A31, S41-F62, D86-V108, Y122-G143, T173-H196, A239-A263, G276-R302	BLIMPS-PRINTS
					P2Y4 purinoceptor signatures: Y32-L48, P111-L126	BLIMPS-PRINTS
					G-protein coupled receptor: DM00013|JN0591|20-336: P3-L305	BLAST-DOMO
					G-protein coupled receptor: DM00013|P53452|17-344: L7-F268	BLAST-DOMO
					G-protein coupled receptor: DM00013|P50406|20-335: G4-L305	BLAST-DOMO
					G-protein coupled receptor: DM00013|P31388|20-336: P3-L305	BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databas s
32	7472019CD1	308	S162 S290 S67 T187 S192 S265	N5 N65	Transmembrane domains: L30-I49, M197-L215	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: G41-Y289	HMMER-PFAM
					G-protein coupled receptor signatures: P90-P129, L206-Y217, L234-K260, T281-K297	BLIMPS-BLOCKS
					G-protein coupled receptor signature: S102-T147	ProfileScan
					Olfactory receptor signatures: I59-Q80, F176-D190, F237-G252, I273-L284, S290-M304	BLIMPS-PRINTS
					Melanocortin receptor family: F51-L63	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily: T26-H50, I59-Q80, S104-I126, V140-L161, I198-A221, K271-K297	BLIMPS-PRINTS
					G-protein coupled receptor: DM00013|P23275|17-306: I17-M304	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23269|15-304: F27-M304	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23266|17-306: I17-M304	BLAST-DOMO
					G-protein coupled receptor: DM00013|S29707|18-306: P21-I300	BLAST-DOMO
					Olfactory receptor PD000921: L165-L244	BLAST-PRODOM
					Olfactory receptor PD149621: T245-M304	BLAST-PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
33	7472021CD1	343	S87 T154 S288 S326 S311 S316	N25 N183 N314	Transmembrane domains: Y55-L75, I214-I234	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: G61-Y310	HMMER-PFAM
					G-protein coupled receptor signatures: S38-L64, G110-P149, P302-K318	BLIMPS-BLOCKS
					G-protein coupled receptor signature: F122-V168	ProfileScan
					G-protein coupled receptor signature: S130-A145	MOTIFS
					Olfactory receptor signatures: M79-Q100, F197-Y211, F258-S273, F297-L305, S311-L325	BLIMPS-PRINTS
					Melanocortin receptor family: V71-L83	BLIMPS-PRINTS
					Vasopressin receptor signature: L75-L86	BLIMPS-PRINTS
					Olfactory receptor PD000921: I186-L265	BLAST-PRODOM
					Olfactory receptor PD149621: V267-E328	BLAST-PRODOM
					G-protein coupled receptor: DM00013|P23269|15-304: E40-L325	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23275|17-306: S38-L325	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23273|18-306: I45-L325	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23266|17-306: S38-S326	BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
34	7472009CD1	323	S87 S232 T290 S8 S67 T193	N5	Transmembrane domains: L30-L47, I201-L221	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: G41-Y289	HMMER-PFAM
					G-protein coupled receptor signatures: K90-P129, L206-Y217, R234-R260, T281-A297	BLIMPS-BLOCKS
					G-protein coupled receptor signature: F102-M147	ProfileScan
					G-protein coupled receptor signature: A110-A125	MOTIFS
					Olfactory receptor signatures: M59-K80, F177-D191, F237-G252, G273-L284, T290-L304	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily: F26-C50, Y104-I126, V140-A161, T198-L221, K271-A297	BLIMPS-PRINTS
					Melanocortin receptor family: I51-L63, I126-N137	BLIMPS-PRINTS
					Vasopressin receptor signature: L55-L66	BLIMPS-PRINTS
					G-protein coupled receptor: DM00013|P23275|17-306: L25-L304	BLAST-DOMO
					G-protein coupled receptor: DM00013|A57069|15-304: L27-L304	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23270|18-311: L25-L304	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23266|17-306: L27-L304	BLAST-DOMO
					Olfactory receptor PD149621: T245-T310	BLAST-PRODOM
					Olfactory receptor PD000921: F168-L244	BLAST-PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
35	7472010CD1	299	T68 S126 S280 T293 S10 S57 T156	N55	Transmembrane domain: L186-I205	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: G31-Y279	HMMER-PFAM
					G-protein coupled receptor signatures: S79-P118, F188-S199, S224-T250, V271-K287	BLIMPS-BLOCKS
					G-protein coupled receptor signature: F91-F135	ProfileScan
					G-protein coupled receptor signature: S99-A114	MOTIFS
					Olfactory receptor signatures: M49-K70, Y166-S180, F227-G242, A263-L274, S280-L294	BLIMPS-PRINTS
					Melanocortin receptor family: I41-L53	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily: Q16-G40, M49-K70, F93-I115, T181-V204, A226-T250, R261-K287	BLIMPS-PRINTS
					G-protein coupled receptor: DM00013|S29709|11-299: G23-L294	BLAST-DOMO
					G-protein coupled receptor: DM00013|S51356|18-307: I24-K292	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23274|18-306: I24-L294	BLAST-DOMO
					G-protein coupled receptor: DM00013|P30955|18-305: I24-L294	BLAST-DOMO
					Olfactory receptor PD149621: V237-R296	BLAST-PRODOM
					Olfactory receptor PD000921: L155-I235	BLAST-PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
36	7472011CD1	307	S87 T288 S193	N5	Transmembrane domains: L23-I43, M98-M118, G204-H228	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: G41-Y287	HMMER-PFAM
					G-protein coupled receptor signatures: K90-P129, R234-R260, T279-Q295	BLIMPS-BLOCKS
					G-protein coupled receptor signature: F102-T148	ProfileScan
					Olfactory receptor signatures: M59-K80, F177-D191, A237-V252, V271-L282, T288-G302	BLIMPS-PRINTS
					Melanocortin receptor family: S51-L63	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily: F26-T50, M59-K80, F104-I126, L140-A161, K199-L222, A236-R260, K269-Q295	BLIMPS-PRINTS
					Olfactory receptor PD000921: L166-I245	BLAST-PRODOM
					Olfactory receptor PD149621: V246-R303	BLAST-PRODOM
					G-protein coupled receptor: DM00013|S29710|15-301: L17-L301	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23275|17-306: L17-L301	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23266|17-306: L17-L301	BLAST-DOMO
					G-protein coupled receptor: DM00013|P47881|20-309: L23-L301	BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
37	7472012CD1	314	T19 S230 S291	N5 N38	7 transmembrane receptor (rhodopsin family) signatures: G41-Y290	HMMER-PFAM
					G-protein coupled receptor signatures: K90-P129, T282-K298	BLIMPS-BLOCKS
					G-protein coupled receptor signature: Y102-M147	ProfileScan
					G-protein coupled receptor signature: M110-A125	MOTIFS
					Olfactory receptor signatures: M59-K80, F177-S191, F238-G253, I274-L285, S291-M305	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily: P26-L50, M59-K80, F104-I126, I199-I222, T237-R261, R272-K298	BLIMPS-PRINTS
					G-protein coupled receptor: DM00013|P23266|17-306: I17-K303	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23274|18-306: E22-K303	BLAST-DOMO
					G-protein coupled receptor: DM00013|S29707|18-306: P21-G299	BLAST-DOMO
					G-protein coupled receptor: DM00013|P30955|18-305: P21-K303	BLAST-DOMO
					Olfactory receptor PD149621: T246-T310	BLAST-PRODOM
					Olfactory receptor PD000921: L166-L245	BLAST-PRODOM

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
38	7472014CD1	310	S19 S67 S93 T267 S18 S137 S290	N5 N265	Transmembrane domains: V30-I46, M59-I78	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: G41-Y289	HMMER-PFAM
					G-protein coupled receptor signatures: K90-P129, I207-Y218, R235-Q261, T281-K297	BLIMPS-BLOCKS
					G-protein coupled receptor signature: Y102-I151	ProfileScan
					G-protein coupled receptor signature: T110-A125	MOTIFS
					Olfactory receptor signatures: M59-K80, F177-S191, F238-G253, A273-L284, S290-M304	BLIMPS-PRINTS
					Melanocortin receptor family: S51-L63	BLIMPS-PRINTS
					Rhodopsin-like GPCR superfamily; P26-R50, M59-K80, F104-I126, V199-L222, Q271-K297	BLIMPS-PRINTS
					Olfactory receptor PD000921: L166-L245	BLAST-PRODOM
					Olfactory receptor PD149621: T246-R306	BLAST-PRODOM
					G-protein coupled receptor: DM00013|P23266|17-306: L17-M304	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23274|18-306: E22-M304	BLAST-DOMO
					G-protein coupled receptor: DM00013|P30955|18-305: D23-M304	BLAST-DOMO
					G-protein coupled receptor: DM00013|P30953|18-306: R20-H305	BLAST-DOMO

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
39	7472020CD1	359	S257 S317 S178 S255	N31	Transmembrane domains: M127-A145, V168-T193	HMMER
					7 transmembrane receptor (rhodopsin family) signatures: R67-Y316	HMMER-PFAM
					G-protein coupled receptor signatures: R116-P155, G233-Y244, S261-T287, T308-Q324	BLIMPS-BLOCKS
					G-protein coupled receptor signature: F129-V173	ProfileScan
					Olfactory receptor signatures: M85-K106, F203-D217, F264-G279, A300-L311, S317-R331	BLIMPS-PRINTS
					GPR orphan receptor signature: S317-W328	BLIMPS-PRINTS
					Cannabinoid receptor signatures: M60-L73, Y316-A326	BLIMPS-PRINTS
					G-protein coupled receptor: DM00013|P23265|17-306: E45-L327	BLAST-DOMO
					G-protein coupled receptor: DM00013|P23268|18-307: S44-L330	BLAST-DOMO
					G-protein coupled receptor: DM00013|S29707|18-306: P47-L327	BLAST-DOMO
					G-protein coupled receptor: DM00013|P30953|18-306: P47-L330	BLAST-DOMO
					Olfactory receptor PD000921: N197-L271	BLAST-PRODOM
					Olfactory receptor PD149621: V273-R333	BLAST-PRODOM

Table 4

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
40	104941CB1	936		g4190944.v113.gs_10.edit	1	936
				104941H1 (BMARNOT02)	208	429
41	1499408CB1	3365		g2335202.v113.gs_4.edit	1	2105
				1499408H1 (SINTBST01)	1068	1325
				927003X11 (BRAINOT04)	1092	1764
				1632960F6 (COLNNOT19)	1613	2099
				4051362F6 (SINTNOT18)	1994	2618
				1426416F6 (SINTBST01)	2223	2686
				2925035F6 (SININOT04)	2535	3043
				927003T6 (BRAINOT04)	2710	3365
42	3168839CB1	1325		3356166H1 (PROSTUT16)	1	281
				g4589937.v113.gs_7.edit	42	1188
				3700658H1 (SININOT05)	160	463
				3168839H1 (BRSTNOT18)	809	1059
				4555080H1 (KERAUNT01)	1084	1325
43	3291235CB1	2124		3291235X308F1 (BONRFET01)	1	413
				g5578925.v113.gs_2.edit	295	2124
				4720927F6 (BRAIHCT02)	315	810
				3291235F6 (BONRFET01)	408	1004
				3370971H1 (CONNTUT05)	955	1208
				1729983H1 (BRSTTUT08)	1073	1293
44	7472001CB1	942		g2121229.v113.gs_4.2.edit	1	942
45	7472003CB1	1197		g3386590.v113.gs_1.edit	1	1197
46	7472004CB1	1110		g4741473.v113.gs_5.edit	1	1110
47	7475687CT1	582		g2121229.v113.gs4.1.nt.edit	1	582
48	7483029CT1	519		g2447218.v113.gs2.nt.edit	1	519
49	7477933CT1	663		g2673897.v113.gs7.nt.edit	1	663
50	7475164CT1	911		g3738097.v113.gs2.nt.edit	1	911
51	7473909CT1	332		g3962498.v113.gs3.nt.edit	1	332
52	7475252CT1	538		g4092817.v113.gs1.nt.edit	1	538
53	7927572CT1	279		g5102597.v113.gs2.nt.edit	1	279
54	7481257CT1	291		g5262456.v113.gs4.nt.edit	1	291
55	7485790CT1	402		g5306302.v113.gs6.nt.edit	1	402
56	7482993CT1	639		g5708153.v113.gs9.nt.edit	1	639

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
57	2829053CB1	1370		170756F1 (BMARNOR02)	1	534
				2829053F6 (TLYMNOT03)	428	989
				6098294H1 (UTRENOT09)	849	1143
				5279076H1 (MUSLNOT01)	1071	1308
				4588915H1 (MASTTXT01)	1132	1370
58	3068234CB1	1567		70489898V1	1	459
				70488597V1	353	883
				5837294H1 (FTUBTUT01)	730	983
				70490272V1	955	1567
59	5029478CB1	1321		6035153H1 (PITUNOT06)	1	582
				6558521H1 (BRAFNON02)	504	1190
				5076961F6 (COLCTUT03)	742	1321
60	5102576CB1	1110		5496406H1 (BRABDIR01)	1	250
				1720010F6 (BLADNOT06)	151	708
				6969401U1	602	710
				5102576F6 (PROSTUS20)	673	1110
61	2200534CB1	1095	1037-1095, 372-491	g2905881.v113.gs_2	1	948
				2200534F6 (SPLNFET02)	534	1095
				576308R6 (BRAVTXT04)	490	1051
62	3275821CB1	1665	1431-1665, 765-1294, 240-597	3275821F6 (PROSBPT06)	1	548
				g3779013.v113.gs_9	265	1665
63	3744167CB1	1609	1184-1238, 249-522	2762536H1 (BRSTNOT12)	745	994
				g5578767.v113.gs_4	262	1338
				3744167H1 (THYMNOT08)	693	977
				g835247	1212	1609
				3474586H1 (LUNGNOT27)	1	309
64	7472007CB1	945		g2431610.v113.gs_4.nt	1	945
65	7472008CB1	1098		g3093312.v113.gs_10.nt	1	1098
66	7472013CB1	954		g4190944.v113.gs_3.nt	1	954
67	7472015CB1	1008		g4467309.v113.gs_2.nt	1	1008
68	7472016CB1	930		g4567182.v113.gs_19.nt	1	930
69	7472017CB1	711		g5262456.v113.gs_7.nt	1	711
70	7472018CB1	1092		g5523795.v113.gs_12.nt	1	1092

Table 4 (cont.)

Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID	Sequence Length	Selected Fragments	Sequence Fragments	5' Position	3' Position
71	7472019CB1	927		g5566548.v113.gs_7.nt	1	927
72	7472021CB1	1032		g5708153.v113.gs_6.nt	1	1032
73	7472009CB1	972		g3213020.v113.gs_4.nt	1	972
74	7472010CB1	900		g3738097.v113.gs_9.nt	1	900
75	7472011CB1	924		g3924656.v113.gs_5.nt	1	924
76	7472012CB1	945		g4190944.v113.gs_1.nt	1	945
77	7472014CB1	933		g4190944.v113.gs_4.nt	1	933
78	7472020CB1	1080		g5706779.v113.gs_3.nt	1	1080

Table 5

Polynucleotide SEQ ID NO:	Incyte Project ID	Representative Library
61	2200534CB1	BRAVTXT04
62	3275821CB1	PROSBPT06
63	3744167CB1	LUNGNOT27

Table 6

Library	Vector	Library Description
BRAVTXT04	PSPORT1	Library was constructed using RNA isolated from separate populations of human astrocytes stimulated for 4 to 6 hours with a combination of cytokines including IL-1. The RNA was pooled for polyA RNA isolation and library construction.
LUNGNOT27	pINCY	Library was constructed using RNA isolated from lung tissue removed from a 17-year-old Hispanic female.
PROSBPT06	pINCY	Library was constructed using RNA isolated from diseased prostate tissue remove from a 66-year-old Caucasian male during a radical prostatectomy and lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated grade 2 (of 4) adenocarcinoma, Gleason grade 3+3. The patient presented with elevated prostate specific antigen (PSA), proteinuria, decreased renal function, and urinary frequency. Patient history included hemiparesis, depressive disorder, sleep apnea, psoriasis, mitral valve prolapse, cerebrovascular disease, benign hypertension, and impotence. Family history included benign hypertension, cerebrovascular disease, and colon cancer.

Table 7

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25:3389-3402.	*ESTs:* Probability value= 1.0E-8 or less *Full Length sequences*: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. USA 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183:63-98; and Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489.	*ESTs:* fasta E value=1.06E-6 *Assembled ESTs*: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less *Full Length sequences:* fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S. and J.G. Henikoff (1991) Nucleic Acids Res. 19:6565-6572; Henikoff, J.G. and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37:417-424.	Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322; Durbin, R. et al. (1998) Our World View, in a Nutshell, Cambridge Univ. Press, pp. 1-350.	*PFAM hits:* Probability value= 1.0E-3 or less *Signal peptide hits:* Score= 0 or greater

Table 7 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, M. et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221.	Normalized quality score≥GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M.S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies.	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12:431-439.	Score=3.5 or greater
TMAP	A program that uses weight matrices to delineate transmembrane segments on protein sequences and determine orientation.	Persson, B. and P. Argos (1994) J. Mol. Biol. 237:182-192; Persson, B. and P. Argos (1996) Protein Sci. 5:363-371.	
TMHMMER	A program that uses a hidden Markov model (HMM) to delineate transmembrane segments on protein sequences and determine orientation.	Sonnhammer, E.L. et al. (1998) Proc. Sixth Intl. Conf. on Intelligent Systems for Mol. Biol., Glasgow et al., eds., The Am. Assoc. for Artificial Intelligence Press, Menlo Park, CA, pp. 175-182.	
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-39,

b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-39,

c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39, and

d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-39.

2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1-39.

3. An isolated polynucleotide encoding a polypeptide of claim 1.

4. An isolated polynucleotide encoding a polypeptide of claim 2.

5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:40-78.

6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

7. A cell transformed with a recombinant polynucleotide of claim 6.

8. A transgenic organism comprising a recombinant polynucleotide of claim 6.

9. A method for producing a polypeptide of claim 1, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

b) recovering the polypeptide so expressed.

10. An isolated antibody which specifically binds to a polypeptide of claim 1.

11. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78,

b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:40-78,

c) a polynucleotide sequence complementary to a),

d) a polynucleotide sequence complementary to b), and

e) an RNA equivalent of a)-d).

12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 11.

13. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.

15. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

16. A composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

17. A composition of claim 16, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-39.

18. A method for treating a disease or condition associated with decreased expression of functional GCREC, comprising administering to a patient in need of such treatment the composition of claim 16.

19. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting agonist activity in the sample.

20. A composition comprising an agonist compound identified by a method of claim 19 and a pharmaceutically acceptable excipient.

21. A method for treating a disease or condition associated with decreased expression of functional GCREC, comprising administering to a patient in need of such treatment a composition of claim 20.

22. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting antagonist activity in the sample.

23. A composition comprising an antagonist compound identified by a method of claim 22 and a pharmaceutically acceptable excipient.

24. A method for treating a disease or condition associated with overexpression of functional GCREC, comprising administering to a patient in need of such treatment a composition of claim 23.

25. A method of screening for a compound that specifically binds to the polypeptide of claim 1, said method comprising the steps of:

a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and

b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a

compound that specifically binds to the polypeptide of claim 1.

26. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, said method comprising:

a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,

b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and

c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.

27. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,

b) detecting altered expression of the target polynucleotide, and

c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound.

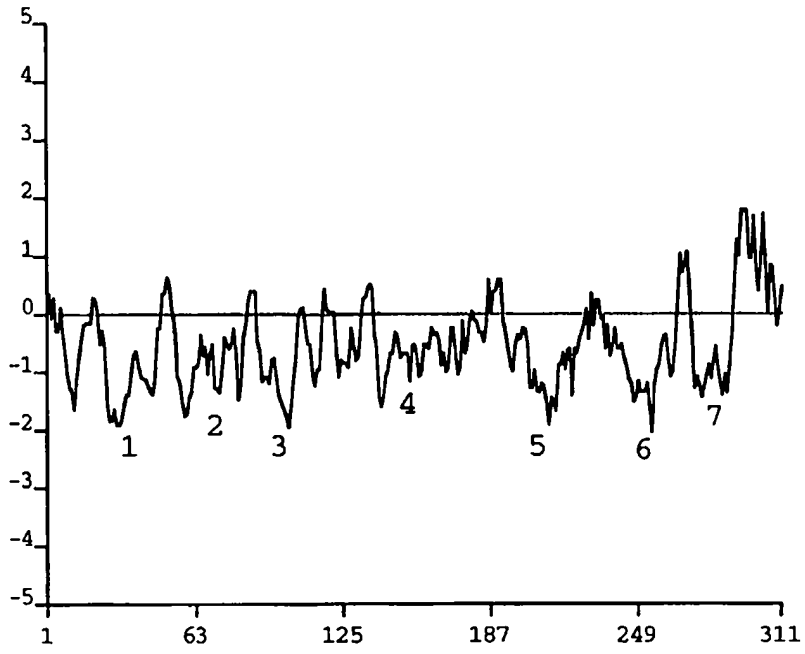
28. A method for assessing toxicity of a test compound, said method comprising:

a) treating a biological sample containing nucleic acids with the test compound;

b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 11 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 11 or fragment thereof;

c) quantifying the amount of hybridization complex; and

d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.



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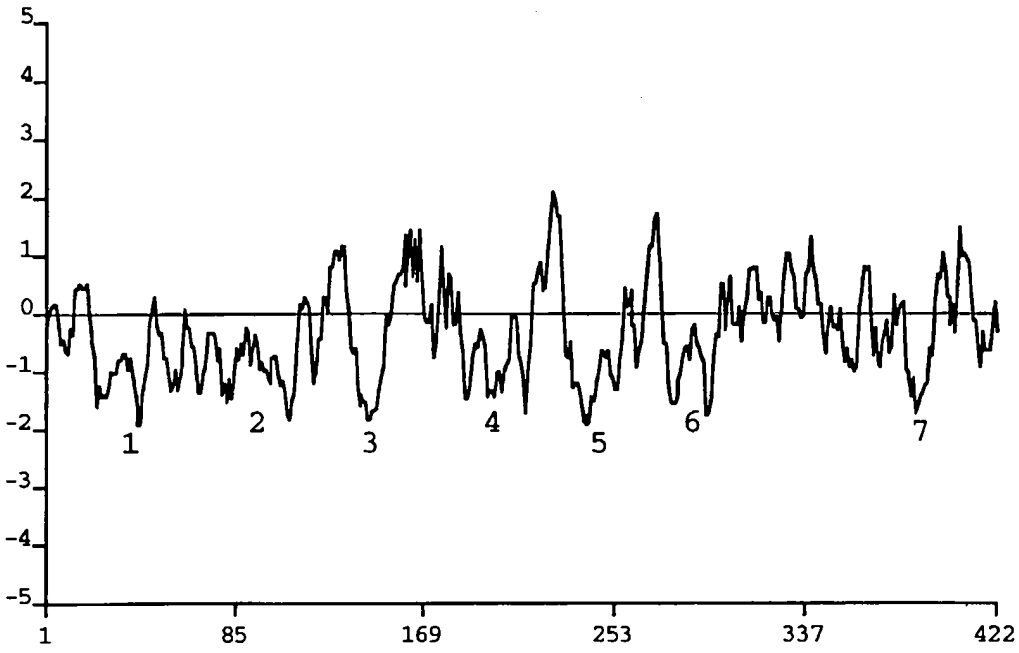

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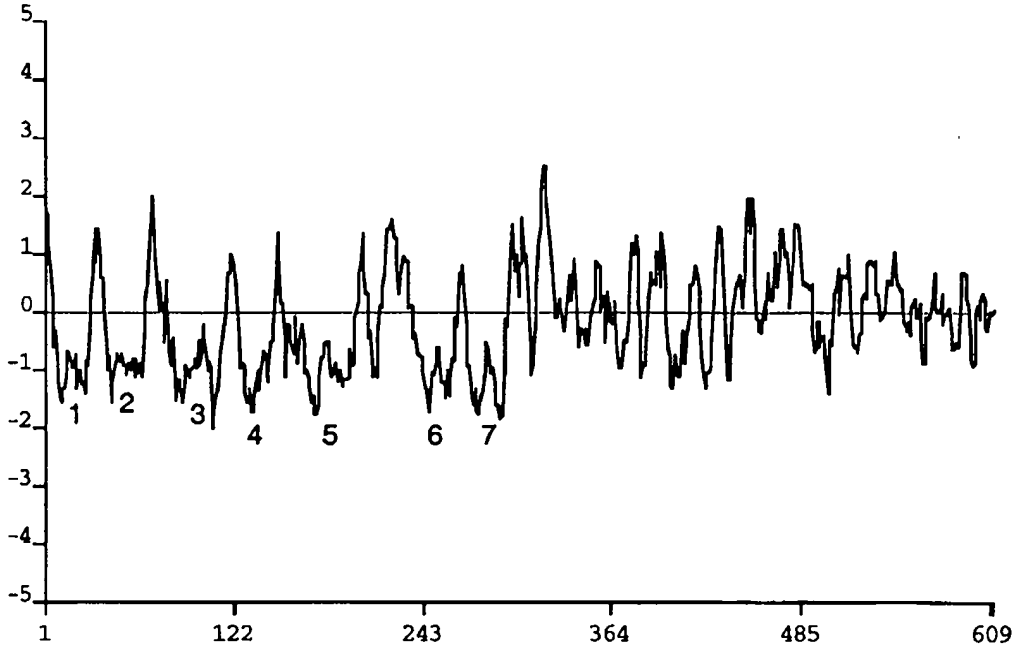

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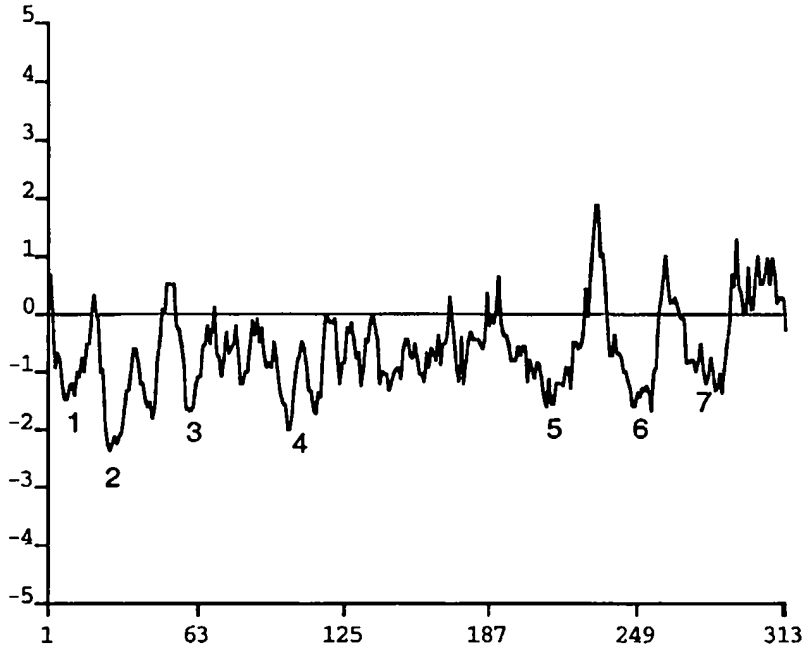

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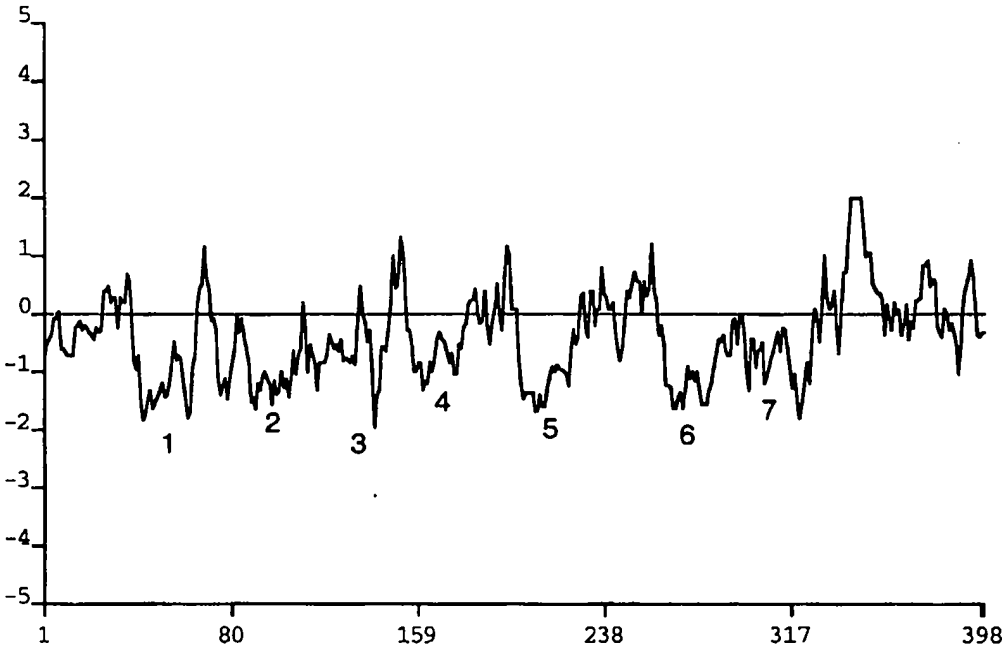

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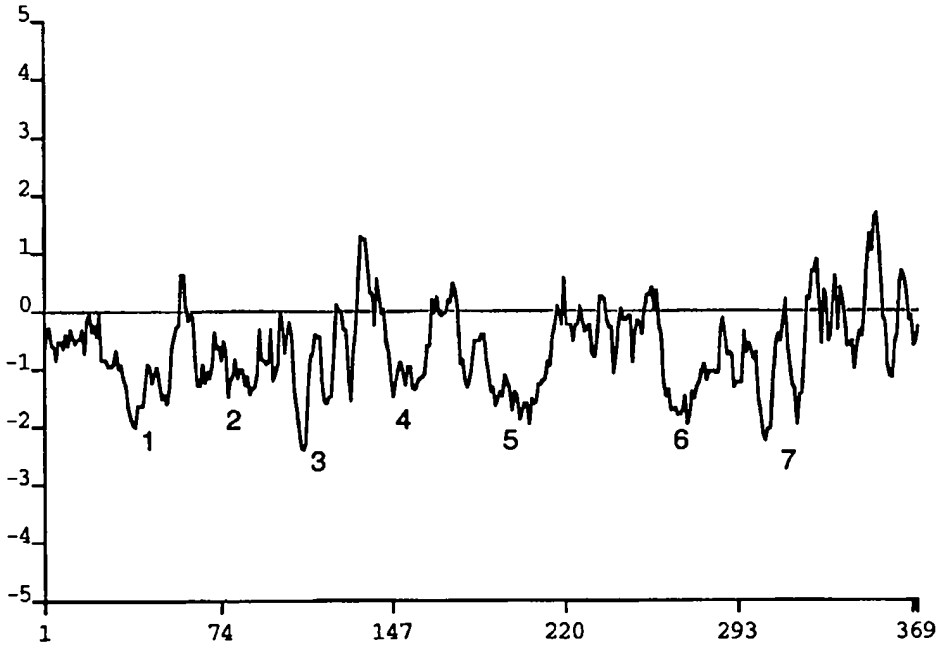

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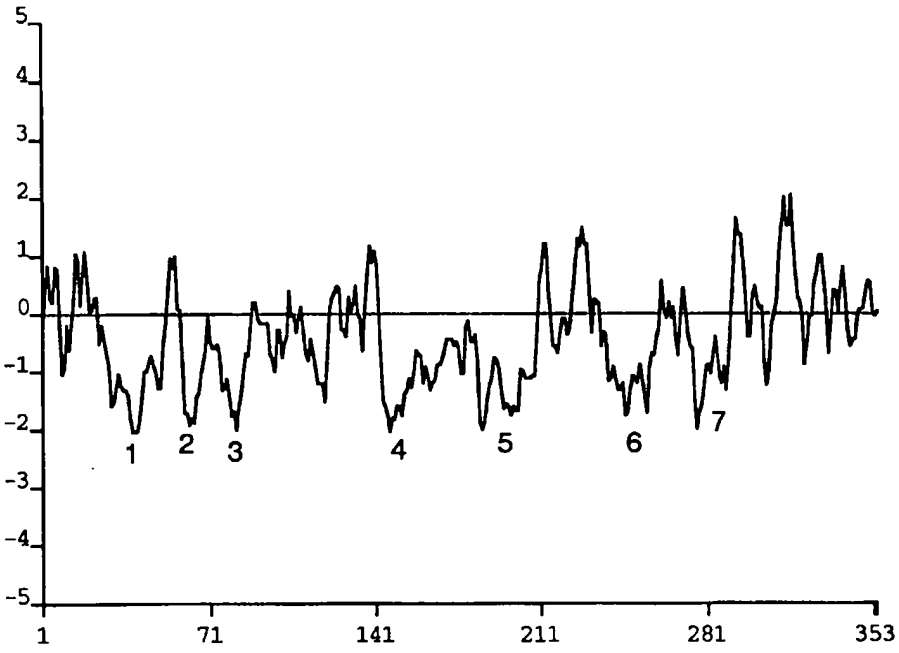

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FIGURE 7

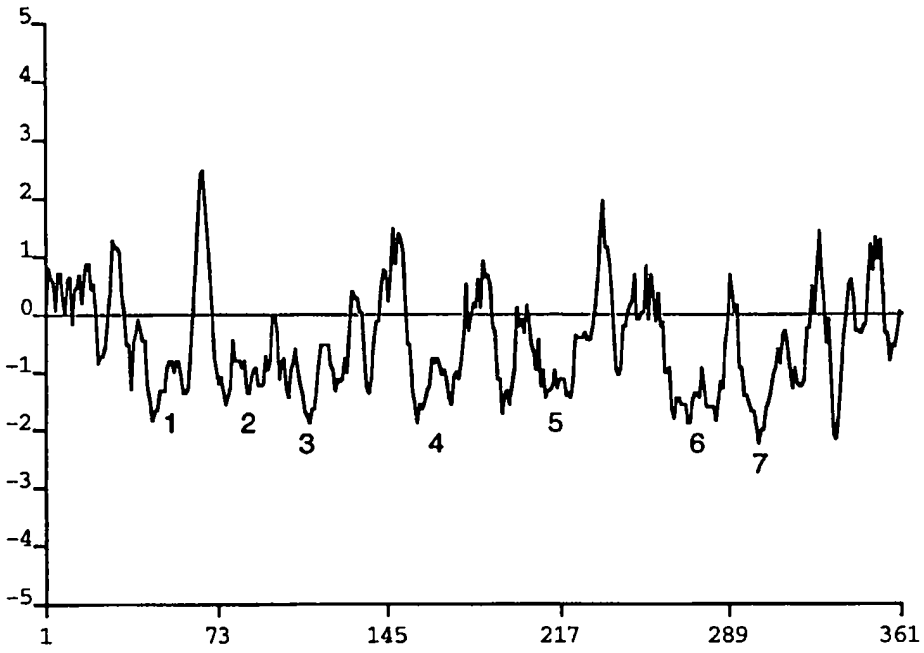

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FIGURE 8

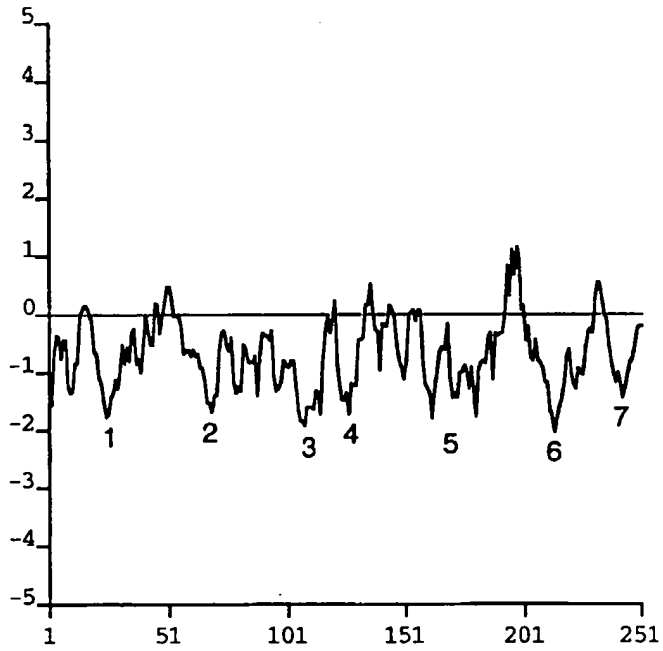

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FIGURE 9

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BURFORD, Neil
BAUGHN, Mariah R.
AU-YOUNG, Janice
YANG, Junming
LU, Dyung Aina M.
REDDY, Roopa

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                530                 535                 540
Pro Ser Ser Ala Gln Arg Ser Pro Gly Pro Arg Pro Ser Ala His
                545                 550                 555
Ser His Ala Gly Ser Leu Arg Pro Gly Leu Ser Ala Ser Trp Gly
                560                 565                 570
Glu Pro Gly Gly Leu Arg Ala Ala Gly Gly Gly Gly Ser Thr Ser
                575                 580                 585
Ser Phe Leu Ser Ser Pro Ser Glu Ser Ser Gly Tyr Ala Thr Leu
                590                 595                 600
His Ser Asp Ser Leu Gly Ser Ala Ser
                605

<210> 5
<211> 313
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472001CD1

<400> 5
Met Glu Arg Ile Asn Ser Thr Leu Leu Thr Ala Phe Ile Leu Thr
  1                 5                  10                  15
Gly Ile Pro Tyr Pro Leu Arg Leu Arg Thr Leu Phe Phe Val Phe
                 20                  25                  30
Phe Phe Leu Ile Tyr Ile Leu Thr Gln Leu Gly Asn Leu Leu Ile
                 35                  40                  45
Leu Ile Thr Val Trp Ala Asp Pro Arg Leu His Ala Arg Pro Met
                 50                  55                  60
Tyr Ile Phe Leu Gly Val Leu Ser Val Ile Asp Met Ser Ile Ser
                 65                  70                  75
Ser Ile Ile Val Pro Arg Leu Met Met Asn Phe Thr Leu Gly Val
                 80                  85                  90
Lys Pro Ile Pro Phe Gly Gly Cys Val Ala Gln Leu Tyr Phe Tyr
                 95                 100                 105
His Phe Leu Gly Ser Thr Gln Cys Phe Leu Tyr Thr Leu Met Ala
                110                 115                 120
Tyr Asp Arg Tyr Leu Ala Ile Cys Gln Pro Leu Arg Tyr Pro Val
                125                 130                 135
Leu Met Thr Ala Lys Leu Ser Ala Leu Leu Val Ala Gly Ala Trp
                140                 145                 150
Met Ala Gly Ser Ile His Gly Ala Leu Gln Ala Ile Leu Thr Phe
                155                 160                 165
Arg Leu Pro Tyr Cys Gly Pro Asn Gln Val Asp Tyr Phe Phe Cys
                170                 175                 180
Asp Ile Pro Ala Val Leu Arg Leu Ala Cys Ala Asp Thr Thr Val
```

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                185                 190                 195
Asn Glu Leu Val Thr Phe Val Asp Ile Gly Val Val Val Ala Ser
                200                 205                 210
Cys Phe Ser Leu Ile Leu Leu Ser Tyr Ile Gln Ile Ile Gln Ala
                215                 220                 225
Ile Leu Arg Ile His Thr Ala Asp Gly Arg Arg Arg Ala Phe Ser
                230                 235                 240
Thr Cys Gly Ala His Val Thr Val Val Thr Val Tyr Tyr Val Pro
                245                 250                 255
Cys Ala Phe Ile Tyr Leu Arg Pro Glu Thr Asn Ser Pro Leu Asp
                260                 265                 270
Gly Ala Ala Ala Leu Val Pro Thr Ala Ile Thr Pro Phe Leu Asn
                275                 280                 285
Pro Leu Ile Tyr Thr Leu Arg Asn Gln Glu Val Lys Leu Ala Leu
                290                 295                 300
Lys Arg Met Leu Arg Ser Pro Arg Thr Pro Ser Glu Val
                305                 310

<210> 6
<211> 398
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472003CD1

<400> 6
Met His Thr Val Ala Thr Ser Gly Pro Asn Ala Ser Trp Gly Ala
  1                 5                  10                  15
Pro Ala Asn Ala Ser Gly Cys Pro Gly Cys Gly Ala Asn Ala Ser
                 20                  25                  30
Asp Gly Pro Val Pro Ser Pro Arg Ala Val Asp Ala Trp Leu Val
                 35                  40                  45
Pro Leu Phe Phe Ala Ala Leu Met Leu Leu Gly Leu Val Gly Asn
                 50                  55                  60
Ser Leu Val Ile Tyr Val Ile Cys Arg His Lys Pro Met Arg Thr
                 65                  70                  75
Val Thr Asn Phe Tyr Ile Ala Asn Leu Ala Ala Thr Asp Val Thr
                 80                  85                  90
Phe Leu Leu Cys Cys Val Pro Phe Thr Ala Leu Leu Tyr Pro Leu
                 95                 100                 105
Pro Gly Trp Val Leu Gly Asp Phe Met Cys Lys Phe Val Asn Tyr
                110                 115                 120
Ile Gln Gln Val Ser Val Gln Ala Thr Cys Ala Thr Leu Thr Ala
                125                 130                 135
Met Ser Val Asp Arg Trp Tyr Val Thr Val Phe Pro Leu Arg Ala
                140                 145                 150
Leu His Arg Arg Thr Pro Arg Leu Ala Leu Ala Val Ser Leu Ser
                155                 160                 165
Ile Trp Thr Gly Ser Ala Ala Val Ser Ala Pro Val Leu Ala Leu
                170                 175                 180
His Arg Leu Ser Pro Gly Pro Arg Ala Tyr Cys Ser Glu Ala Phe
                185                 190                 195
Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn Leu Leu
                200                 205                 210
Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr Ala
                215                 220                 225
Ala Met Leu Arg His Leu Gly Arg Val Ala Val Arg Pro Ala Pro
                230                 235                 240
Ala Asp Ser Ala Leu Gln Gly Gln Val Leu Ala Glu Arg Ala Gly
                245                 250                 255
Ala Val Arg Ala Lys Val Ser Arg Leu Val Ala Ala Val Val Leu
                260                 265                 270
Leu Phe Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu
                275                 280                 285
Gln Ala Leu Gly Pro Ala Gly Ser Trp His Pro Arg Ser Tyr Ala
```

```
                290                 295                 300
Ala Tyr Ala Leu Lys Thr Trp Ala His Cys Met Ser Tyr Ser Asn
                305                 310                 315
Ser Ala Leu Asn Pro Leu Leu Tyr Ala Phe Leu Gly Ser His Phe
                320                 325                 330
Arg Gln Ala Phe Arg Arg Val Cys Pro Cys Ala Pro Arg Arg Pro
                335                 340                 345
Arg Arg Pro Arg Arg Pro Gly Pro Ser Asp Pro Ala Ala Pro His
                350                 355                 360
Ala Glu Leu Leu Arg Leu Gly Ser His Pro Ala Pro Ala Arg Ala
                365                 370                 375
Gln Lys Pro Gly Ser Ser Gly Leu Ala Ala Arg Gly Leu Cys Val
                380                 385                 390
Leu Gly Glu Asp Asn Ala Pro Leu
                395
```

<210> 7
<211> 369
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472004CD1

```
<400> 7
Met Ala Pro Thr Gly Leu Ser Ser Leu Thr Val Asn Ser Thr Ala
  1               5                  10                  15
Val Pro Thr Thr Pro Ala Ala Phe Lys Ser Leu Asn Leu Pro Leu
                 20                  25                  30
Gln Ile Thr Leu Ser Ala Ile Met Ile Phe Ile Leu Phe Val Ser
                 35                  40                  45
Phe Leu Gly Asn Leu Val Val Cys Leu Met Val Tyr Gln Lys Ala
                 50                  55                  60
Ala Met Arg Ser Ala Ile Asn Ile Leu Leu Ala Ser Leu Ala Phe
                 65                  70                  75
Ala Asp Met Leu Leu Ala Val Leu Asn Met Pro Phe Ala Leu Val
                 80                  85                  90
Thr Ile Leu Thr Thr Arg Trp Ile Phe Gly Lys Phe Phe Cys Arg
                 95                 100                 105
Val Ser Ala Met Phe Phe Trp Leu Phe Val Ile Glu Gly Val Ala
                110                 115                 120
Ile Leu Leu Ile Ile Ser Ile Asp Arg Phe Leu Ile Ile Val Gln
                125                 130                 135
Arg Gln Asp Lys Leu Asn Pro Tyr Arg Ala Lys Val Leu Ile Ala
                140                 145                 150
Val Ser Trp Ala Thr Ser Phe Cys Val Ala Phe Pro Leu Ala Val
                155                 160                 165
Gly Asn Pro Asp Leu Gln Ile Pro Ser Arg Ala Pro Gln Cys Val
                170                 175                 180
Phe Gly Tyr Thr Thr Asn Pro Gly Tyr Gln Ala Tyr Val Ile Leu
                185                 190                 195
Ile Ser Leu Ile Ser Phe Phe Ile Pro Phe Leu Val Ile Leu Tyr
                200                 205                 210
Ser Phe Met Gly Ile Leu Asn Thr Leu Arg His Asn Ala Leu Arg
                215                 220                 225
Ile His Ser Tyr Pro Glu Gly Ile Cys Leu Ser Gln Ala Ser Lys
                230                 235                 240
Leu Gly Leu Met Ser Leu Gln Arg Pro Phe Gln Met Ser Ile Asp
                245                 250                 255
Met Gly Phe Lys Thr Arg Ala Phe Thr Thr Ile Leu Ile Leu Phe
                260                 265                 270
Ala Val Phe Ile Val Cys Trp Ala Pro Phe Thr Thr Tyr Ser Leu
                275                 280                 285
Val Ala Thr Phe Ser Lys His Phe Tyr Tyr Gln His Asn Phe Phe
                290                 295                 300
Glu Ile Ser Thr Trp Leu Leu Trp Leu Cys Tyr Leu Lys Ser Ala
```

```
                305                 310                 315
Leu Asn Pro Leu Ile Tyr Tyr Trp Arg Ile Lys Lys Phe His Asp
                320                 325                 330
Ala Cys Leu Asp Met Met Pro Lys Ser Phe Lys Phe Leu Pro Gln
                335                 340                 345
Leu Pro Gly His Thr Lys Arg Arg Ile Arg Pro Ser Ala Val Tyr
                350                 355                 360
Val Cys Gly Glu His Arg Thr Val Val
                365
```

<210> 8
<211> 194
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7475687CP1

<400> 8

```
Met Ala Tyr Asp Arg Tyr Leu Ala Ile Cys Gln Pro Leu Arg Tyr
  1               5                  10                  15
Pro Val Leu Met Asn Gly Arg Leu Cys Thr Val Leu Val Ala Gly
                20                  25                  30
Ala Trp Val Ala Gly Ser Met His Gly Ser Ile Gln Ala Thr Leu
                35                  40                  45
Thr Phe Arg Leu Pro Tyr Cys Gly Pro Asn Gln Val Asp Tyr Phe
                50                  55                  60
Ile Cys Asp Ile Pro Ala Val Leu Arg Leu Ala Cys Ala Asp Thr
                65                  70                  75
Thr Val Asn Glu Leu Val Thr Phe Val Asp Ile Gly Val Val Ala
                80                  85                  90
Ala Ser Cys Phe Met Leu Ile Leu Leu Ser Tyr Ala Asn Ile Val
                95                 100                 105
Asn Ala Ile Leu Lys Ile Arg Thr Thr Asp Gly Arg Arg Arg Ala
               110                 115                 120
Phe Ser Thr Cys Gly Ser His Leu Ile Val Val Thr Val Tyr Tyr
               125                 130                 135
Val Pro Cys Ile Phe Ile Tyr Leu Arg Ala Gly Ser Lys Gly Pro
               140                 145                 150
Leu Asp Gly Ala Ala Ala Val Phe Tyr Thr Val Val Thr Pro Leu
               155                 160                 165
Leu Asn Pro Leu Ile Tyr Thr Leu Arg Asn Gln Glu Val Lys Ser
               170                 175                 180
Ala Leu Lys Arg Ile Thr Ala Gly Gln Ala Asp Val Asn Asn
               185                 190
```

<210> 9
<211> 173
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7483029CP1

<400> 9

```
Met Tyr Leu Val Thr Val Leu Gly Asn Leu Leu Ile Ile Leu Ala
  1               5                  10                  15
Thr Ile Ser Asp Ser His Leu His Thr Pro Met Tyr Phe Phe Leu
                20                  25                  30
Ser Asn Leu Ser Phe Ala Asp Ile Cys Phe Val Ser Thr Thr Val
                35                  40                  45
Pro Lys Met Leu Val Asn Ile Gln Thr Gln Ser Arg Val Ile Thr
                50                  55                  60
Tyr Ala Asp Cys Ile Thr Gln Met Cys Phe Phe Ile Leu Phe Val
                65                  70                  75
```

```
Val Leu Asp Ser Leu Leu Leu Thr Val Met Ala Tyr Asp Arg Phe
                 80                  85                  90
Val Ala Ile Cys His Pro Leu His Tyr Thr Val Ile Met Asn Ser
                 95                 100                 105
Trp Leu Cys Gly Leu Leu Val Leu Val Ser Trp Ile Val Ser Ile
                110                 115                 120
Leu Tyr Ser Leu Leu Gln Ser Ile Met Ala Leu Gln Leu Ser Phe
                125                 130                 135
Cys Thr Glu Leu Lys Ile Pro His Phe Phe Cys Glu Leu Asn Gln
                140                 145                 150
Val Ile His Leu Ala Cys Ser Asp Thr Phe Ile Asn Asp Met Met
                155                 160                 165
Met Asn Phe Thr Ser Val Leu Leu
                170
```

<210> 10
<211> 220
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7477933CP1

<400> 10

```
Pro Met Tyr Phe Phe Leu Ser Asn Leu Cys Trp Ala Asp Ile Gly
  1                  5                  10                  15
Leu Thr Ser Ala Thr Val Pro Lys Val Ile Leu Asp Met Gln Ser
                 20                  25                  30
His Ser Arg Val Ile Ser His Val Gly Cys Leu Thr Gln Met Ser
                 35                  40                  45
Phe Leu Val Leu Phe Ala Cys Ile Glu Gly Met Leu Leu Thr Val
                 50                  55                  60
Met Ala Tyr Gly Cys Phe Val Ala Ile Cys Arg Pro Leu His Tyr
                 65                  70                  75
Pro Val Ile Val Asn Pro His Leu Cys Val Phe Phe Val Leu Val
                 80                  85                  90
Ser Phe Phe Leu Asn Leu Leu Asp Ser Gln Leu His Ser Trp Ile
                 95                 100                 105
Val Leu Gln Phe Thr Ile Ile Lys Asn Val Glu Ile Ser Asn Phe
                110                 115                 120
Phe Cys Asp Pro Ser Gln Leu Leu Asn Leu Ala Cys Ser Asp Ser
                125                 130                 135
Val Ile Asn Ser Ile Phe Ile Tyr Phe Asp Ser Thr Met Phe Gly
                140                 145                 150
Phe Leu Pro Ile Ser Gly Ile Leu Leu Ser Tyr Tyr Lys Ile Val
                155                 160                 165
Pro Ser Ile Leu Arg Met Ser Ser Ser Asp Gly Lys Tyr Lys Ala
                170                 175                 180
Phe Ser Thr Tyr Gly Ser His Leu Gly Val Val Cys Trp Phe Tyr
                185                 190                 195
Gly Thr Val Ile Gly Met Tyr Leu Ala Ser Ala Val Ser Pro Pro
                200                 205                 210
Pro Arg Asn Gly Val Val Ala Ser Val Met
                215                 220
```

<210> 11
<211> 302
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7475164CP1

<400> 11

```
Ala Glu Phe Ile Leu Ala Gly Leu Thr Gln Arg Pro Glu Leu Gln
```

```
  1               5                  10                  15
Leu Pro Leu Phe Leu Leu Phe Leu Gly Ile Tyr Val Val Thr Val
                20                  25                  30
Val Gly Asn Leu Gly Met Ile Phe Leu Ile Ala Leu Ser Ser Gln
                35                  40                  45
Leu Tyr Pro Pro Val Tyr Tyr Phe Leu Ser His Leu Ser Phe Ile
                50                  55                  60
Asp Leu Cys Tyr Ser Ser Val Ile Thr Pro Lys Met Leu Val Asn
                65                  70                  75
Phe Val Pro Glu Glu Asn Ile Ile Ser Phe Leu Glu Cys Ile Thr
                80                  85                  90
Gln Leu Tyr Phe Phe Leu Ile Phe Val Ile Ala Glu Gly Tyr Leu
                95                 100                 105
Leu Thr Ala Met Glu Tyr Asp Arg Tyr Val Ala Ile Cys Arg Pro
               110                 115                 120
Leu Leu Tyr Asn Ile Val Met Ser His Arg Val Cys Ser Ile Met
               125                 130                 135
Met Ala Val Val Tyr Ser Leu Gly Phe Leu Trp Ala Thr Val His
               140                 145                 150
Thr Thr Arg Met Ser Val Leu Ser Phe Cys Arg Ser His Thr Val
               155                 160                 165
Ser His Tyr Phe Cys Asp Ile Leu Pro Leu Leu Thr Leu Ser Cys
               170                 175                 180
Ser Ser Thr His Ile Asn Glu Ile Leu Leu Phe Ile Ile Gly Gly
               185                 190                 195
Val Asn Thr Leu Ala Thr Thr Leu Ala Val Leu Ile Ser Tyr Ala
               200                 205                 210
Phe Ile Phe Ser Ser Ile Leu Gly Ile His Ser Thr Glu Gly Gln
               215                 220                 225
Ser Lys Ala Phe Gly Thr Cys Ser Ser His Leu Leu Ala Val Gly
               230                 235                 240
Ile Phe Phe Gly Ser Ile Thr Phe Met Tyr Phe Lys Pro Pro Ser
               245                 250                 255
Ser Thr Thr Met Glu Lys Glu Lys Val Ser Ser Val Phe Tyr Ile
               260                 265                 270
Thr Ile Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn
               275                 280                 285
Lys Asp Val Lys Asn Ala Leu Lys Lys Met Thr Arg Gly Arg Gln
               290                 295                 300
Ser Ser
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<210> 12
<211> 110
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7473909CP1

<400> 12

```
Gly Pro Arg Thr Ala Ser Gly Cys Val Ile Met Ile Cys Phe Ala
  1               5                  10                  15
Leu Thr Val Leu Ser Tyr Ile Arg Ile Leu Ala Thr Val Val Gln
                20                  25                  30
Ile Arg Ser Ala Ala Ser Arg Arg Lys Ala Phe Ser Thr Cys Ser
                35                  40                  45
Ser His Leu Gly Met Val Leu Leu Phe Tyr Gly Thr Gly Ser Ser
                50                  55                  60
Thr Tyr Met Arg Pro Thr Thr Arg Tyr Ser Pro Leu Glu Gly Arg
                65                  70                  75
Leu Ala Ala Val Phe Tyr Ser Ile Leu Ile Pro Thr Leu Asn Pro
                80                  85                  90
Leu Ile Tyr Ser Leu Arg Asn Gln Asp Met Lys Arg Ala Leu Trp
                95                 100                 105
Lys Leu Tyr Leu Gln
```

110

<210> 13
<211> 178
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7475252CP1

<400> 13
Glu Pro Glu Asn Leu Thr Gly Val Leu Glu Phe Leu Leu Leu Gly
1 5 10 15
Leu Pro Asp Asp Pro Glu Leu Gln Pro Val Leu Phe Gly Leu Phe
20 25 30
Leu Ser Met Tyr Leu Val Met Val Leu Gly Asn Leu Leu Ile Ile
35 40 45
Leu Ala Val Ser Ser Asp Ser His Leu His Ser Pro Met Tyr Phe
50 55 60
Phe Leu Ser Asn Leu Ser Leu Ala Asp Ile Gly Phe Ala Ser Thr
65 70 75
Thr Val Pro Lys Met Ile Val Asp Ile Gln Ala His Ser Arg Leu
80 85 90
Ile Ser Tyr Val Gly Cys Leu Thr Gln Met Ser Phe Leu Ile Phe
95 100 105
Phe Ala Cys Met Glu Ser Leu Leu Leu Ile Val Met Ala Tyr Asp
110 115 120
Arg Phe Val Ala Ile Cys His Pro Leu His Tyr Gln Val Ile Met
125 130 135
Ser Pro Arg Leu Cys Gly Phe Leu Val Leu Val Ser Phe Phe Leu
140 145 150
Ser Leu Leu Asp Ser Gln Leu His Asn Leu Ile Val Leu Gln Leu
155 160 165
Thr Cys Phe Asn Asp Val Glu Ile Ser Asn Phe Phe Leu
170 175

<210> 14
<211> 92
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7927572CP1

<400> 14
Leu Leu Asp Ala Gln Leu Tyr Asn Leu Ile Ala Leu Gln Met Thr
1 5 10 15
Cys Phe Lys Asp Val Glu Ile Pro Asn Phe Phe Cys Asp Pro Ser
20 25 30
Gln Leu Pro His Leu Ala Cys Cys Asp Thr Phe Asn Asn Asn Ile
35 40 45
Ile Leu Tyr Phe Pro Asp Ala Ile Phe Gly Phe Leu Pro Ile Ser
50 55 60
Gly Thr Leu Phe Ser Tyr Asp Lys Ile Val Ser Ser Ile Leu Arg
65 70 75
Val Ser Ser Ser Gly Gly Lys Tyr Lys Ala Phe Ser Thr Tyr Gly
80 85 90
Ser His

<210> 15
<211> 97
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7481257CP1

<400> 15
Met Glu Val Thr Thr Phe Ala Met Cys Leu Ile Ile Val Leu Val
1 5 10 15
Pro Leu Leu Leu Ile Leu Val Ser Tyr Gly Phe Ile Ala Val Ala
20 25 30
Val Leu Lys Ile Lys Ser Ala Ala Gly Arg Gln Lys Ala Phe Gly
35 40 45
Thr Cys Ser Ser His Leu Val Val Val Ser Ile Phe Cys Gly Thr
50 55 60
Val Thr Tyr Met Tyr Ile Gln Pro Gly Asn Ser Pro Asn Gln Asn
65 70 75
Glu Gly Lys Leu Leu Ser Ile Phe Tyr Ser Ile Val Thr Pro Ser
80 85 90
Leu Asn Pro Leu Ile Tyr Thr
95

<210> 16
<211> 133
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7485790CP1

<400> 16
Asp Pro Glu Leu Gln Pro Ile Leu Ala Gly Leu Ser Leu Ser Met
1 5 10 15
Tyr Leu Val Thr Val Leu Arg Asn Leu Leu Ile Ser Leu Ala Val
20 25 30
Ser Ser Asp Ser His Leu His Thr Pro Met Cys Phe Phe Leu Ser
35 40 45
Asn Leu Cys Trp Ala Asp Ile Gly Phe Thr Ser Ala Thr Val Pro
50 55 60
Lys Met Ile Val Asp Met Arg Ser His Ser Gly Val Ile Ser Tyr
65 70 75
Ala Asp Cys Leu Thr Arg Met Ser Phe Leu Val Leu Phe Ala Cys
80 85 90
Val Glu Asp Met Leu Leu Thr Val Met Ala Tyr Asp Cys Phe Val
95 100 105
Ala Ile Cys Arg Pro Leu His Tyr Pro Val Ile Val Asn Pro His
110 115 120
Leu Cys Val Phe Leu Val Ser Val Ser Phe Ser Leu Ala
125 130

<210> 17
<211> 213
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7482993CP1

<400> 17
Gly Ser Glu Cys Leu Leu Leu Ala Ala Met Ala Tyr Asp Arg Tyr
1 5 10 15
Ile Ala Ile Cys Asn Pro Leu Arg Tyr Ser Val Ile Leu Ser Lys
20 25 30
Val Leu Cys Asn Gln Leu Ala Ala Ser Cys Trp Ala Ala Gly Phe
35 40 45
Leu Asn Ser Val Val His Thr Val Leu Thr Phe Cys Leu Pro Phe
50 55 60

```
Cys Gly Asn Asn Gln Ile Asn Tyr Phe Phe Cys Asp Ile Pro Pro
                65                  70                  75
Leu Leu Ile Leu Ser Cys Gly Asn Thr Ser Val Asn Glu Leu Ala
                80                  85                  90
Leu Leu Ser Thr Gly Val Phe Ile Gly Trp Thr Pro Phe Leu Cys
                95                 100                 105
Ile Val Leu Ser Tyr Ile Cys Ile Ile Ser Thr Ile Leu Arg Ile
               110                 115                 120
Gln Ser Ser Glu Gly Arg Arg Lys Ala Phe Ser Thr Cys Ala Ser
               125                 130                 135
His Leu Ala Ile Val Phe Leu Phe Tyr Gly Ser Ala Ile Phe Thr
               140                 145                 150
Tyr Val Arg Pro Ile Ser Thr Tyr Ser Leu Lys Lys Asp Arg Leu
               155                 160                 165
Val Ser Val Leu Tyr Ser Val Val Thr Pro Met Leu Asn Pro Ile
               170                 175                 180
Ile Tyr Thr Leu Arg Asn Lys Asp Ile Lys Glu Ala Val Lys Thr
               185                 190                 195
Ile Gly Ser Lys Trp Gln Pro Pro Ile Ser Ser Leu Asp Ser Lys
               200                 205                 210
Leu Thr Tyr
```

<210> 18
<211> 180
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2829053CD1

<400> 18

```
Met Ser Glu Ala Ala Thr Arg Trp Ser Cys Gln Gly Ser Cys Gln
  1                 5                  10                  15
Lys Thr Cys Phe Ser Arg Val Arg Pro Trp Arg Arg Arg Cys Ser
                20                  25                  30
Cys Gly Asp Ser Ser Ser Arg Arg Arg Arg Ser Cys Cys Thr Gly
                35                  40                  45
Ser Leu Gly Pro Met Pro Arg Leu Pro Ser Leu Trp Pro Leu Ser
                50                  55                  60
Leu Pro Leu Arg Ser Leu Ser Ser Pro His Arg Val Gln Gly Leu
                65                  70                  75
Gly Pro Pro Arg Arg Leu Lys Ser Gln Leu Leu Pro Arg Phe Phe
                80                  85                  90
Trp Arg Arg Gln Gln Glu Pro Leu Ser Ser Phe Pro Gly Arg Asn
                95                 100                 105
Glu Gly Gly Ser Glu Met Glu Ile Leu Gly Val Cys Pro Val Ser
               110                 115                 120
Pro Gly Ala Leu Ser Tyr Met Glu Ser Pro Thr Gly Phe Trp Arg
               125                 130                 135
Pro Arg Glu Ala Ser Ser Leu Glu Leu Ala Lys Gly Ile Ser Lys
               140                 145                 150
Arg Arg His Phe Leu Pro Ala Pro Ala Leu Cys Pro Asn Pro Arg
               155                 160                 165
Ser Ser Glu Ala Phe Pro Gly Ala Val Cys Val Thr Leu Ala Ile
               170                 175                 180
```

<210> 19
<211> 353
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3068234CD1

<400> 19
Met Asn Glu Cys His Tyr Asp Lys His Met Asp Phe Phe Tyr Asn
1 5 10 15
Arg Ser Asn Thr Asp Thr Val Asp Asp Trp Thr Gly Thr Lys Leu
20 25 30
Val Ile Val Leu Cys Val Gly Thr Phe Phe Cys Leu Phe Ile Phe
35 40 45
Phe Ser Asn Ser Leu Val Ile Ala Ala Val Ile Lys Asn Arg Lys
50 55 60
Phe His Phe Pro Phe Tyr Tyr Leu Leu Ala Asn Leu Ala Ala Ala
65 70 75
Asp Phe Phe Ala Gly Ile Ala Tyr Val Phe Leu Met Phe Asn Thr
80 85 90
Gly Pro Val Ser Lys Thr Leu Thr Val Asn Arg Trp Phe Leu Arg
95 100 105
Gln Gly Leu Leu Asp Ser Ser Leu Thr Ala Ser Leu Thr Asn Leu
110 115 120
Leu Val Ile Ala Val Glu Arg His Met Ser Ile Met Arg Met Arg
125 130 135
Val His Ser Asn Leu Thr Lys Lys Arg Val Thr Leu Leu Ile Leu
140 145 150
Leu Val Trp Ala Ile Ala Ile Phe Met Gly Ala Val Pro Thr Leu
155 160 165
Gly Trp Asn Cys Leu Cys Asn Ile Ser Ala Cys Ser Ser Leu Ala
170 175 180
Pro Ile Tyr Ser Arg Ser Tyr Leu Val Phe Trp Thr Val Ser Asn
185 190 195
Leu Met Ala Phe Leu Ile Met Val Val Val Tyr Leu Arg Ile Tyr
200 205 210
Val Tyr Val Lys Arg Lys Thr Asn Val Leu Ser Pro His Thr Ser
215 220 225
Gly Ser Ile Ser Arg Arg Arg Thr Pro Met Lys Leu Met Lys Thr
230 235 240
Val Met Thr Val Leu Gly Ala Phe Val Val Cys Trp Thr Pro Gly
245 250 255
Leu Val Val Leu Leu Leu Asp Gly Leu Asn Cys Arg Gln Cys Gly
260 265 270
Val Gln His Val Lys Arg Trp Phe Leu Leu Leu Ala Leu Leu Asn
275 280 285
Ser Val Val Asn Pro Ile Ile Tyr Ser Tyr Lys Asp Glu Asp Met
290 295 300
Tyr Gly Thr Met Lys Lys Met Ile Cys Cys Phe Ser Gln Glu Asn
305 310 315
Pro Glu Arg Arg Pro Ser Arg Ile Pro Ser Thr Val Leu Ser Arg
320 325 330
Ser Asp Thr Gly Ser Gln Tyr Ile Glu Asp Ser Ile Ser Gln Gly
335 340 345
Ala Val Cys Asn Lys Ser Thr Ser
350

<210> 20
<211> 361
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 5029478CD1

<400> 20
Met Ser Pro Glu Cys Ala Arg Ala Ala Gly Asp Ala Pro Leu Arg
1 5 10 15
Ser Leu Glu Gln Ala Asn Arg Thr Arg Phe Pro Phe Phe Ser Asp
20 25 30
Val Lys Gly Asp His Arg Leu Val Leu Ala Ala Val Glu Thr Thr
35 40 45
Val Leu Val Leu Ile Phe Ala Val Ser Leu Leu Gly Asn Val Cys

```
                50                  55                  60
Ala Leu Val Leu Val Ala Arg Arg Arg Arg Arg Gly Ala Thr Ala
                65                  70                  75
Cys Leu Val Leu Asn Leu Phe Cys Ala Asp Leu Leu Phe Ile Ser
                80                  85                  90
Ala Ile Pro Leu Val Leu Ala Val Arg Trp Thr Glu Ala Trp Leu
                95                  100                 105
Leu Gly Pro Val Ala Cys His Leu Leu Phe Tyr Val Met Thr Leu
                110                 115                 120
Ser Gly Ser Val Thr Ile Leu Thr Leu Ala Ala Val Ser Leu Glu
                125                 130                 135
Arg Met Val Cys Ile Val His Leu Gln Arg Gly Val Arg Gly Pro
                140                 145                 150
Gly Arg Arg Ala Arg Ala Val Leu Leu Ala Leu Ile Trp Gly Tyr
                155                 160                 165
Ser Ala Val Ala Ala Leu Pro Leu Cys Val Phe Phe Arg Val Val
                170                 175                 180
Pro Gln Arg Leu Pro Gly Ala Asp Gln Glu Ile Ser Ile Cys Thr
                185                 190                 195
Leu Ile Trp Pro Thr Ile Pro Gly Glu Ile Ser Trp Asp Val Ser
                200                 205                 210
Phe Val Thr Leu Asn Phe Leu Val Pro Gly Leu Val Ile Val Ile
                215                 220                 225
Ser Tyr Ser Lys Ile Leu Gln Ile Thr Lys Ala Ser Arg Lys Arg
                230                 235                 240
Leu Thr Val Ser Leu Ala Tyr Ser Glu Ser His Gln Ile Arg Val
                245                 250                 255
Ser Gln Gln Asp Phe Arg Leu Phe Arg Thr Leu Phe Leu Leu Met
                260                 265                 270
Val Ser Phe Phe Ile Met Trp Ser Pro Ile Ile Ile Thr Ile Leu
                275                 280                 285
Leu Ile Leu Ile Gln Asn Phe Lys Gln Asp Leu Val Ile Trp Pro
                290                 295                 300
Ser Leu Phe Phe Trp Val Val Ala Phe Thr Phe Ala Asn Ser Ala
                305                 310                 315
Leu Asn Pro Ile Leu Tyr Asn Met Thr Leu Cys Arg Asn Glu Trp
                320                 325                 330
Lys Lys Ile Phe Cys Cys Phe Trp Phe Pro Glu Lys Gly Ala Ile
                335                 340                 345
Leu Thr Asp Thr Ser Val Lys Arg Asn Asp Leu Ser Ile Ile Ser
                350                 355                 360
Gly
```

<210> 21
<211> 251
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 5102576CD1

<400> 21

```
Met Tyr Leu Val Thr Val Leu Arg Asn Leu Phe Ser Ile Leu Ala
  1                 5                  10                  15
Val Ser Ser Asp Cys Pro Leu His Thr Pro Met Tyr Phe Phe Leu
                20                  25                  30
Ser Asn Leu Cys Trp Pro Asp Ile Gly Phe Thr Ser Ala Met Val
                35                  40                  45
Pro Lys Met Ile Val Asp Thr Gln Ser His Ser Arg Val Ile Ser
                50                  55                  60
His Ala Gly Cys Leu Thr Gln Met Ser Phe Leu Leu Leu Val Ala
                65                  70                  75
Cys Ile Glu Gly Met Leu Leu Thr Val Met Ala Tyr Asp Cys Phe
                80                  85                  90
Val Ala Ile Cys Arg Pro Leu His Tyr Pro Val Ile Val Asn Pro
```

```
                95                  100                 105
His Leu Cys Val Phe Phe Val Leu Val Ser Phe Phe Leu Ser Leu
                110                 115                 120
Leu Asp Ser Gln Leu His Ser Trp Ile Val Leu Gln Leu Thr Ile
                125                 130                 135
Ile Lys Asn Val Glu Ile Ser Asn Leu Val Cys Asp Pro Ser Gln
                140                 145                 150
Leu Leu Asn Leu Ala Cys Ser Asp Ser Val Ile Asn Asn Ile Phe
                155                 160                 165
Ile Tyr Phe Asp Ser Thr Met Phe Gly Phe Leu Pro Ile Ser Gly
                170                 175                 180
Ile Phe Leu Ser Tyr Tyr Lys Ile Val Pro Ser Ile Leu Arg Ile
                185                 190                 195
Ser Ser Ser Asp Gly Lys Tyr Lys Ala Phe Ser Thr Cys Gly Cys
                200                 205                 210
His Leu Ala Val Val Cys Trp Phe Tyr Gly Thr Gly Ile Gly Met
                215                 220                 225
Tyr Leu Thr Ser Ala Val Ser Pro Pro Pro Arg Asn Gly Val Val
                230                 235                 240
Ala Ser Val Met Tyr Ala Val Val Thr Pro Cys
                245                 250

<210> 22
<211> 315
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2200534CD1

<400> 22
Met Lys Ala Asn Tyr Ser Ala Glu Glu Arg Phe Leu Leu Leu Gly
  1               5                  10                  15
Phe Ser Asp Trp Pro Ser Leu Gln Pro Val Leu Phe Ala Leu Val
                20                  25                  30
Leu Leu Cys Tyr Leu Leu Thr Leu Thr Gly Asn Ser Ala Leu Val
                35                  40                  45
Leu Leu Ala Val Arg Asp Pro Arg Leu His Thr Pro Met Tyr Tyr
                50                  55                  60
Phe Leu Cys His Leu Ala Leu Val Asp Ala Gly Phe Thr Thr Ser
                65                  70                  75
Val Val Pro Pro Leu Leu Ala Asn Leu Arg Gly Pro Ala Leu Trp
                80                  85                  90
Leu Pro Arg Ser His Cys Thr Ala Gln Leu Cys Ala Ser Leu Ala
                95                  100                 105
Leu Gly Ser Ala Glu Cys Val Leu Leu Ala Val Met Ala Leu Asp
                110                 115                 120
Arg Ala Ala Ala Val Cys Arg Pro Leu Arg Tyr Ala Gly Leu Val
                125                 130                 135
Ser Pro Arg Leu Cys Arg Thr Leu Ala Ser Ala Ser Trp Leu Ser
                140                 145                 150
Gly Leu Thr Asn Ser Val Ala Gln Thr Ala Leu Leu Ala Glu Arg
                155                 160                 165
Pro Leu Cys Ala Pro Arg Leu Leu Asp His Phe Ile Cys Glu Leu
                170                 175                 180
Pro Ala Leu Leu Lys Leu Ala Cys Gly Gly Asp Gly Asp Thr Thr
                185                 190                 195
Glu Asn Gln Met Phe Ala Ala Arg Val Val Ile Leu Leu Leu Pro
                200                 205                 210
Phe Ala Val Ile Leu Ala Ser Tyr Gly Ala Val Ala Arg Ala Val
                215                 220                 225
Cys Cys Met Arg Phe Ser Gly Gly Arg Arg Arg Ala Val Gly Thr
                230                 235                 240
Cys Gly Ser His Leu Thr Ala Val Cys Leu Phe Tyr Gly Ser Ala
                245                 250                 255
Ile Tyr Thr Tyr Leu Gln Pro Ala Gln Arg Tyr Asn Gln Ala Arg
```

```
                260                 265                 270
Gly Lys Phe Val Ser Leu Phe Tyr Thr Val Val Thr Pro Ala Leu
                275                 280                 285
Asn Pro Leu Ile Tyr Thr Leu Arg Asn Lys Lys Val Lys Gly Ala
                290                 295                 300
Ala Arg Arg Leu Leu Arg Ser Leu Gly Arg Gly Gln Ala Gly Gln
                305                 310                 315
```

<210> 23
<211> 470
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3275821CD1

<400> 23

```
Met Asp Thr Thr Met Glu Ala Asp Leu Gly Ala Thr Gly His Arg
  1               5                  10                  15
Pro Arg Thr Glu Leu Asp Asp Glu Asp Ser Tyr Pro Gln Gly Gly
                 20                  25                  30
Trp Asp Thr Val Phe Leu Val Ala Leu Leu Leu Leu Gly Leu Pro
                 35                  40                  45
Ala Asn Gly Leu Met Ala Trp Leu Ala Gly Ser Gln Ala Arg His
                 50                  55                  60
Gly Ala Gly Thr Arg Leu Ala Leu Leu Leu Leu Ser Leu Ala Leu
                 65                  70                  75
Ser Asp Phe Leu Phe Leu Ala Ala Ala Ala Phe Gln Ile Leu Glu
                 80                  85                  90
Ile Arg His Gly Gly His Trp Pro Leu Gly Thr Ala Ala Cys Arg
                 95                 100                 105
Phe Tyr Tyr Phe Leu Trp Gly Val Ser Tyr Ser Ser Gly Leu Phe
                110                 115                 120
Leu Leu Ala Ala Leu Ser Leu Asp Arg Cys Leu Leu Ala Leu Cys
                125                 130                 135
Pro His Trp Tyr Pro Gly His Arg Pro Val Arg Leu Pro Leu Trp
                140                 145                 150
Val Cys Ala Gly Val Trp Val Leu Ala Thr Leu Phe Ser Val Pro
                155                 160                 165
Trp Leu Val Phe Pro Glu Ala Ala Val Trp Trp Tyr Asp Leu Val
                170                 175                 180
Ile Cys Leu Asp Phe Trp Asp Ser Glu Glu Leu Ser Leu Arg Met
                185                 190                 195
Leu Glu Val Leu Gly Gly Phe Leu Pro Phe Leu Leu Leu Leu Val
                200                 205                 210
Cys His Val Leu Thr Gln Ala Thr Ala Cys Arg Thr Cys His Arg
                215                 220                 225
Gln Gln Gln Pro Ala Ala Cys Arg Gly Phe Ala Arg Val Ala Arg
                230                 235                 240
Thr Ile Leu Ser Ala Tyr Val Val Leu Arg Leu Pro Tyr Gln Leu
                245                 250                 255
Ala Gln Leu Leu Tyr Leu Ala Phe Leu Trp Asp Val Tyr Ser Gly
                260                 265                 270
Tyr Leu Leu Trp Glu Ala Leu Val Tyr Ser Asp Tyr Leu Ile Leu
                275                 280                 285
Leu Asn Ser Cys Leu Ser Pro Phe Leu Cys Leu Met Ala Ser Ala
                290                 295                 300
Asp Leu Arg Thr Leu Leu Arg Ser Val Leu Ser Ser Phe Ala Ala
                305                 310                 315
Ala Leu Cys Glu Glu Arg Pro Gly Ser Phe Thr Pro Thr Glu Pro
                320                 325                 330
Gln Thr Gln Leu Asp Ser Glu Gly Pro Thr Leu Pro Glu Pro Met
                335                 340                 345
Ala Glu Ala Gln Ser Gln Met Asp Pro Val Ala Gln Pro Gln Val
                350                 355                 360
```

```
Asn Pro Thr Leu Gln Pro Arg Ser Asp Pro Thr Ala Gln Pro Gln
                365                 370                 375
Leu Asn Pro Thr Ala Gln Pro Gln Ser Asp Pro Thr Ala Gln Pro
                380                 385                 390
Gln Leu Asn Leu Met Ala Gln Pro Gln Ser Asp Ser Val Ala Gln
                395                 400                 405
Pro Gln Ala Asp Thr Asn Val Gln Thr Pro Ala Pro Ala Ala Ser
                410                 415                 420
Ser Val Pro Ser Pro Cys Asp Glu Ala Ser Pro Thr Pro Ser Ser
                425                 430                 435
His Pro Thr Pro Gly Ala Leu Glu Asp Pro Ala Thr Pro Pro Ala
                440                 445                 450
Ser Glu Gly Glu Ser Pro Ser Ser Thr Pro Pro Glu Ala Ala Pro
                455                 460                 465
Gly Ala Gly Pro Thr
                470

<210> 24
<211> 358
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3744167CD1

<400> 24
Met Ser Val Cys Tyr Arg Pro Pro Gly Asn Glu Thr Leu Leu Ser
  1                 5                  10                  15
Trp Lys Thr Ser Arg Ala Thr Gly Thr Ala Phe Leu Leu Leu Ala
                 20                  25                  30
Ala Leu Leu Gly Leu Pro Gly Asn Gly Phe Val Val Trp Ser Leu
                 35                  40                  45
Ala Gly Trp Arg Pro Ala Arg Gly Arg Pro Leu Ala Ala Thr Leu
                 50                  55                  60
Val Leu His Leu Ala Leu Ala Asp Gly Ala Val Leu Leu Leu Thr
                 65                  70                  75
Pro Leu Phe Val Ala Phe Leu Thr Arg Gln Ala Trp Pro Leu Gly
                 80                  85                  90
Gln Ala Gly Cys Lys Ala Val Tyr Tyr Val Cys Ala Leu Ser Met
                 95                 100                 105
Tyr Ala Ser Val Leu Leu Thr Gly Leu Leu Ser Leu Gln Arg Cys
                110                 115                 120
Leu Ala Val Thr Arg Pro Phe Leu Ala Pro Arg Leu Arg Ser Pro
                125                 130                 135
Ala Leu Ala Arg Arg Leu Leu Leu Ala Val Trp Leu Ala Ala Leu
                140                 145                 150
Leu Leu Ala Val Pro Ala Ala Val Tyr Arg His Leu Trp Arg Asp
                155                 160                 165
Arg Val Cys Gln Leu Cys His Pro Ser Pro Val His Ala Ala Ala
                170                 175                 180
His Leu Ser Leu Glu Thr Leu Thr Ala Phe Val Leu Pro Phe Gly
                185                 190                 195
Leu Met Leu Gly Cys Tyr Ser Val Thr Leu Ala Arg Leu Arg Gly
                200                 205                 210
Ala Arg Trp Gly Ser Gly Arg His Gly Ala Arg Val Gly Arg Leu
                215                 220                 225
Val Ser Ala Ile Val Leu Ala Phe Gly Leu Leu Trp Ala Pro Tyr
                230                 235                 240
His Ala Val Asn Leu Leu Gln Ala Val Ala Ala Leu Ala Pro Pro
                245                 250                 255
Glu Gly Ala Leu Ala Lys Leu Gly Gly Ala Gly Gln Ala Ala Arg
                260                 265                 270
Ala Gly Thr Thr Ala Leu Ala Phe Phe Ser Ser Ser Val Asn Pro
                275                 280                 285
Val Leu Tyr Val Phe Thr Ala Gly Asp Leu Leu Pro Arg Ala Gly
                290                 295                 300
```

```
Pro Arg Phe Leu Thr Arg Leu Phe Glu Gly Ser Gly Glu Ala Arg
                305                 310                 315
Gly Gly Gly Arg Ser Arg Glu Gly Thr Met Glu Leu Arg Thr Thr
                320                 325                 330
Pro Gln Leu Lys Val Val Gly Gln Gly Arg Gly Asn Gly Asp Pro
                335                 340                 345
Gly Gly Gly Met Glu Lys Asp Gly Pro Glu Trp Asp Leu
                350                 355
```

<210> 25
<211> 314
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472007CD1

<400> 25

```
Met Trp Glu Asn Trp Thr Ile Val Ser Glu Phe Val Leu Val Ser
  1                 5                  10                  15
Phe Ser Ala Leu Ser Thr Glu Leu Gln Ala Leu Leu Phe Leu Leu
                 20                  25                  30
Phe Leu Thr Ile Tyr Leu Val Thr Leu Met Gly Asn Val Leu Ile
                 35                  40                  45
Ile Leu Val Thr Ile Ala Asp Ser Ala Leu Gln Ser Pro Met Tyr
                 50                  55                  60
Phe Phe Leu Arg Asn Leu Ser Phe Leu Glu Ile Gly Phe Asn Leu
                 65                  70                  75
Val Ile Val Pro Lys Met Leu Gly Thr Leu Ile Ile Gln Asp Thr
                 80                  85                  90
Thr Ile Ser Phe Leu Gly Cys Ala Thr Gln Met Tyr Phe Phe Phe
                 95                 100                 105
Phe Phe Gly Ala Ala Glu Cys Cys Leu Leu Ala Thr Met Ala Tyr
                110                 115                 120
Asp Arg Tyr Val Ala Ile Cys Asp Pro Leu His Tyr Pro Val Ile
                125                 130                 135
Met Gly His Ile Ser Cys Ala Gln Leu Ala Ala Ala Ser Trp Phe
                140                 145                 150
Ser Gly Phe Ser Val Ala Thr Val Gln Thr Thr Trp Ile Phe Ser
                155                 160                 165
Phe Pro Phe Cys Gly Pro Asn Arg Val Asn His Phe Phe Cys Asp
                170                 175                 180
Ser Pro Pro Val Ile Ala Leu Val Cys Ala Asp Thr Ser Val Phe
                185                 190                 195
Glu Leu Glu Ala Leu Thr Ala Thr Val Pro Phe Ile Leu Phe Pro
                200                 205                 210
Phe Leu Leu Ile Leu Gly Ser Tyr Val Arg Ile Leu Ser Thr Ile
                215                 220                 225
Phe Arg Met Pro Ser Ala Glu Gly Lys His Gln Ala Phe Ser Thr
                230                 235                 240
Cys Ser Ala His Leu Leu Val Val Ser Leu Phe Tyr Ser Thr Ala
                245                 250                 255
Ile Leu Thr Tyr Phe Arg Pro Gln Ser Ser Ala Ser Ser Glu Ser
                260                 265                 270
Lys Lys Leu Leu Ser Leu Ser Ser Thr Val Val Thr Pro Met Leu
                275                 280                 285
Asn Pro Ile Ile Tyr Ser Ser Arg Asn Lys Glu Val Lys Ala Ala
                290                 295                 300
Leu Lys Arg Leu Ile His Arg Thr Leu Gly Ser Gln Lys Leu
                305                 310
```

<210> 26
<211> 365
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472008CD1

<400> 26
Met Glu Gly Ser Val Glu Ala Thr Pro Glu Ile Pro Ala Gln Met
1 5 10 15
Lys Cys His Pro Ser Arg Pro Ser Thr Leu Asn Gln Leu Ser Phe
20 25 30
Tyr Gly Ala Val Ser Ser Leu Gly Arg Met His Gly Leu Glu Thr
35 40 45
Lys Ser Ser Ala Glu Ile Arg Ala Gly Leu Lys Arg Cys Asp Thr
50 55 60
Leu Val Leu Glu Ala Ser Thr Leu Glu Gly Asn Met Val Ile Val
65 70 75
Leu Val Ser Leu Lys Asp Pro Lys Leu His Ile Pro Met Tyr Phe
80 85 90
Phe Leu Ser Asn Leu Ser Leu Val Asp Leu Cys Leu Thr Ser Ser
95 100 105
Cys Val Pro Gln Met Leu Ile Asn Phe Trp Gly Pro Glu Lys Thr
110 115 120
Ile Ser Tyr Ile Gly Cys Ala Ile Gln Leu Tyr Val Phe Leu Trp
125 130 135
Leu Gly Ala Thr Glu Tyr Val Leu Leu Val Val Met Ala Val Asp
140 145 150
Cys Tyr Val Ala Val Cys His Pro Leu Gln Asn Thr Met Ile Met
155 160 165
His Pro Lys Leu Cys Leu Gln Leu Ala Ile Leu Ala Trp Gly Thr
170 175 180
Gly Leu Ala Gln Ser Leu Ile Gln Ser Pro Ala Thr Leu Arg Leu
185 190 195
Pro Phe Cys Ser Gln Arg Met Val Asp Asp Val Val Cys Glu Val
200 205 210
Pro Ala Leu Ile Gln Leu Ser Ser Thr Asp Thr Thr Tyr Ser Glu
215 220 225
Ile Gln Met Ser Ile Ala Ser Val Val Leu Leu Val Met Pro Leu
230 235 240
Ile Ile Ile Leu Ser Ser Ser Gly Ala Ile Ala Lys Ala Val Leu
245 250 255
Arg Ile Lys Ser Thr Ala Gly Gln Lys Lys Ala Phe Gly Thr Cys
260 265 270
Ile Ser His Leu Leu Val Val Ser Leu Phe Tyr Gly Thr Val Thr
275 280 285
Gly Val Tyr Leu Gln Pro Lys Asn His Tyr Pro His Glu Trp Gly
290 295 300
Lys Phe Leu Thr Leu Phe Tyr Thr Val Val Thr Pro Thr Leu Asn
305 310 315
Pro Leu Ile Tyr Thr Leu Arg Asn Lys Glu Leu His Pro Trp Leu
320 325 330
Lys Glu Ala Lys Val Gln Thr Ala Ser Glu Ser Ala Ser Pro Lys
335 340 345
His Trp Gln Leu Pro His Gly Val Gly Pro Val Gly Val Gln Lys
350 355 360
Thr Arg Thr Glu Leu
365

<210> 27
<211> 317
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472013CD1

<400> 27
Met Ser Phe Ala Pro Asn Ala Ser His Ser Pro Val Phe Leu Leu

```
  1               5                  10                  15
Leu Gly Phe Ser Arg Ala Asn Ile Ser Tyr Thr Leu Leu Phe Phe
             20                  25                  30
Leu Phe Leu Ala Ile Tyr Leu Thr Thr Ile Leu Gly Asn Val Thr
             35                  40                  45
Leu Val Leu Leu Ile Ser Trp Asp Ser Arg Leu His Ser Pro Met
             50                  55                  60
Tyr Tyr Leu Leu Arg Gly Leu Ser Val Ile Asp Met Gly Leu Ser
             65                  70                  75
Thr Val Thr Leu Pro Gln Leu Leu Ala His Leu Val Ser His Tyr
             80                  85                  90
Pro Thr Ile Pro Ala Ala Arg Cys Leu Ala Gln Phe Phe Phe Phe
             95                  100                 105
Tyr Ala Phe Gly Val Thr Asp Thr Leu Val Ile Ala Val Met Ala
             110                 115                 120
Leu Asp Arg Tyr Val Ala Ile Cys Asp Pro Leu His Tyr Ala Leu
             125                 130                 135
Val Met Asn His Gln Arg Cys Ala Cys Leu Leu Ala Leu Ser Trp
             140                 145                 150
Val Val Ser Ile Leu His Thr Met Leu Arg Val Gly Leu Val Leu
             155                 160                 165
Pro Leu Cys Trp Thr Gly Asp Ala Gly Gly Asn Val Asn Leu Pro
             170                 175                 180
His Phe Phe Cys Asp His Arg Pro Leu Leu Arg Ala Ser Cys Ser
             185                 190                 195
Asp Ile His Ser Asn Glu Leu Ala Ile Phe Phe Glu Gly Gly Phe
             200                 205                 210
Leu Met Leu Gly Pro Cys Ala Leu Ile Val Leu Ser Tyr Val Arg
             215                 220                 225
Ile Gly Ala Ala Ile Leu Arg Leu Pro Ser Ala Ala Gly Arg Arg
             230                 235                 240
Arg Ala Val Ser Thr Cys Gly Ser His Leu Thr Met Val Gly Phe
             245                 250                 255
Leu Tyr Gly Thr Ile Ile Cys Val Tyr Phe Gln Pro Pro Phe Gln
             260                 265                 270
Asn Ser Gln Tyr Gln Asp Met Val Ala Ser Val Met Tyr Thr Ala
             275                 280                 285
Ile Thr Pro Leu Ala Asn Pro Phe Val Tyr Ser Leu His Asn Lys
             290                 295                 300
Asp Val Lys Gly Ala Leu Cys Arg Leu Leu Glu Trp Val Lys Val
             305                 310                 315
Asp Pro
```

<210> 28
<211> 335
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472015CD1

<400> 28

```
Met Glu Ser Ser Phe Ser Phe Gly Val Ile Leu Ala Val Leu Ala
  1               5                  10                  15
Ser Leu Ile Ile Ala Thr Asn Thr Leu Val Ala Val Ala Val Leu
             20                  25                  30
Leu Leu Ile His Lys Asn Asp Gly Val Ser Leu Cys Phe Thr Leu
             35                  40                  45
Asn Leu Ala Val Ala Asp Thr Leu Ile Gly Val Ala Ile Ser Gly
             50                  55                  60
Leu Leu Thr Asp Gln Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys
             65                  70                  75
Thr Leu Cys Ser Leu Arg Met Ala Phe Val Thr Ser Ser Ala Ala
             80                  85                  90
Ala Ser Val Leu Thr Val Met Leu Ile Thr Phe Asp Arg Tyr Leu
```

```
                 95                  100                 105
Ala Ile Lys Gln Pro Phe Arg Tyr Leu Lys Ile Met Ser Gly Phe
                110                 115                 120
Val Ala Gly Ala Cys Ile Ala Gly Leu Trp Leu Val Ser Tyr Leu
                125                 130                 135
Ile Gly Phe Leu Pro Leu Gly Ile Pro Met Phe Gln Gln Thr Ala
                140                 145                 150
Tyr Lys Gly Gln Cys Ser Phe Phe Ala Val Phe His Pro His Phe
                155                 160                 165
Val Leu Thr Leu Ser Cys Val Gly Phe Phe Pro Ala Met Leu Leu
                170                 175                 180
Phe Val Phe Phe Tyr Cys Asp Met Leu Lys Ile Ala Ser Met His
                185                 190                 195
Ser Gln Gln Ile Arg Lys Met Glu His Ala Gly Ala Met Ala Gly
                200                 205                 210
Gly Tyr Arg Ser Pro Arg Thr Pro Ser Asp Phe Lys Ala Leu Arg
                215                 220                 225
Thr Val Ser Val Leu Ile Gly Ser Phe Ala Leu Ser Trp Thr Pro
                230                 235                 240
Phe Leu Ile Thr Gly Ile Val Gln Val Ala Cys Gln Glu Cys His
                245                 250                 255
Leu Tyr Leu Val Leu Glu Arg Tyr Leu Trp Leu Leu Gly Val Gly
                260                 265                 270
Asn Ser Leu Leu Asn Pro Leu Ile Tyr Ala Tyr Trp Gln Lys Glu
                275                 280                 285
Val Arg Leu Gln Leu Tyr His Met Ala Leu Gly Val Lys Lys Val
                290                 295                 300
Leu Thr Ser Phe Leu Leu Phe Leu Ser Ala Arg Asn Cys Gly Pro
                305                 310                 315
Glu Arg Pro Arg Glu Ser Ser Cys His Ile Val Thr Ile Ser Ser
                320                 325                 330
Ser Glu Phe Asp Gly
                335

<210> 29
<211> 309
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472016CD1

<400> 29
Met Arg Glu Asn Asn Gln Ser Ser Thr Leu Glu Phe Ile Leu Leu
  1               5                  10                  15
Gly Val Thr Gly Gln Gln Glu Gln Glu Asp Phe Phe Tyr Ile Leu
                20                  25                  30
Phe Leu Phe Ile Tyr Pro Ile Thr Leu Ile Gly Asn Leu Leu Ile
                35                  40                  45
Val Leu Ala Ile Cys Ser Asp Val Arg Leu His Asn Pro Met Tyr
                50                  55                  60
Phe Leu Leu Ala Asn Leu Ser Leu Val Asp Ile Phe Phe Ser Ser
                65                  70                  75
Val Thr Ile Pro Lys Met Leu Ala Asn His Leu Leu Gly Ser Lys
                80                  85                  90
Ser Ile Ser Phe Gly Gly Cys Leu Thr Gln Met Tyr Phe Met Ile
                95                 100                 105
Ala Leu Gly Asn Thr Asp Ser Tyr Ile Leu Ala Ala Met Ala Tyr
                110                 115                 120
Asp Arg Ala Val Ala Ile Ser His Pro Leu His Tyr Thr Thr Ile
                125                 130                 135
Met Ser Pro Arg Ser Cys Ile Trp Leu Ile Ala Gly Ser Trp Val
                140                 145                 150
Ile Gly Asn Ala Asn Ala Leu Pro His Thr Leu Leu Thr Ala Ser
                155                 160                 165
Leu Ser Phe Cys Gly Asn Gln Glu Val Ala Asn Phe Tyr Cys Asp
```

```
                170                 175                 180
Ile Thr Pro Leu Leu Lys Leu Ser Cys Ser Asp Ile His Phe His
                185                 190                 195
Val Lys Met Met Tyr Leu Gly Val Gly Ile Phe Ser Val Pro Leu
                200                 205                 210
Leu Cys Ile Ile Val Ser Tyr Ile Arg Val Phe Ser Thr Val Phe
                215                 220                 225
Gln Val Pro Ser Thr Lys Gly Val Leu Lys Ala Phe Ser Thr Cys
                230                 235                 240
Gly Ser His Leu Thr Val Val Ser Leu Tyr Tyr Gly Thr Val Met
                245                 250                 255
Gly Thr Tyr Phe Arg Pro Leu Thr Asn Tyr Ser Leu Lys Asp Ala
                260                 265                 270
Val Ile Thr Val Met Tyr Thr Ala Val Thr Pro Met Leu Asn Pro
                275                 280                 285
Phe Ile Tyr Ser Leu Arg Asn Arg Asp Met Lys Ala Ala Leu Arg
                290                 295                 300
Lys Leu Phe Asn Lys Arg Ile Ser Ser
                305
```

<210> 30
<211> 236
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472017CD1

```
<400> 30
Met Gly Met Thr Asn Ser Ser Val Lys Gly Asp Phe Ile Leu Leu
  1                 5                  10                  15
Leu Trp Asn Leu Lys Gly Pro Asp Lys Thr Ile Thr Phe Leu Gly
                 20                  25                  30
Cys Val Ile Gln Leu Tyr Ile Ser Leu Ala Leu Gly Ser Thr Glu
                 35                  40                  45
Cys Val Leu Leu Ala Val Met Ala Phe Asp Arg Tyr Ala Ala Val
                 50                  55                  60
Cys Lys Pro Leu His Tyr Thr Ala Val Met Asn Pro Gln Leu Cys
                 65                  70                  75
Gln Ala Leu Ala Gly Val Ala Trp Leu Ser Gly Val Gly Asn Thr
                 80                  85                  90
Leu Ile Gln Gly Thr Val Thr Leu Trp Leu Pro Arg Cys Gly His
                 95                 100                 105
Arg Leu Leu Gln His Phe Phe Leu Ala Cys Val Asp Ile His Asp
                110                 115                 120
Asn Glu Val Gln Leu Phe Val Ala Ser Leu Val Leu Leu Leu Leu
                125                 130                 135
Pro Leu Val Leu Ile Leu Leu Ser Tyr Gly His Ile Ala Lys Val
                140                 145                 150
Val Ile Arg Ile Lys Ser Val Gln Ala Trp Cys Lys Gly Leu Gly
                155                 160                 165
Thr Cys Gly Ser His Leu Ile Val Val Ser Leu Phe Cys Gly Thr
                170                 175                 180
Ile Thr Ala Val Tyr Ile Gln Ser Asn Ser Ser Tyr Ala His Ala
                185                 190                 195
His Gly Lys Phe Ile Ser Leu Phe Tyr Thr Val Val Thr Pro Thr
                200                 205                 210
Leu Asn Pro Leu Ile Tyr Thr Leu Arg Asn Asn Asp Val Lys Gly
                215                 220                 225
Ala Leu Arg Leu Phe Asn Arg Asp Leu Gly Thr
                230                 235
```

<210> 31
<211> 363
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472018CD1

<400> 31
Met Gly Pro Gly Glu Ala Leu Leu Ala Gly Leu Leu Val Met Val
1 5 10 15
Leu Ala Val Ala Leu Leu Ser Asn Ala Leu Val Leu Leu Cys Cys
20 25 30
Ala Tyr Ser Ala Glu Leu Arg Thr Arg Ala Ser Gly Val Leu Leu
35 40 45
Val Asn Leu Ser Leu Gly His Leu Leu Leu Ala Ala Leu Asp Met
50 55 60
Pro Phe Thr Leu Leu Gly Val Met Arg Gly Arg Thr Pro Ser Ala
65 70 75
Pro Gly Ala Cys Gln Val Ile Gly Phe Leu Asp Thr Phe Leu Ala
80 85 90
Ser Asn Ala Ala Leu Ser Val Ala Ala Leu Ser Ala Asp Gln Trp
95 100 105
Leu Ala Val Gly Phe Pro Leu Arg Tyr Ala Gly Arg Leu Arg Pro
110 115 120
Arg Tyr Ala Gly Leu Leu Leu Gly Cys Ala Trp Gly Gln Ser Leu
125 130 135
Ala Phe Ser Gly Ala Ala Leu Gly Cys Ser Trp Leu Gly Tyr Ser
140 145 150
Ser Ala Phe Ala Ser Cys Ser Leu Arg Leu Pro Pro Glu Pro Glu
155 160 165
Arg Pro Arg Phe Ala Ala Phe Thr Ala Thr Leu His Ala Val Gly
170 175 180
Phe Val Leu Pro Leu Ala Val Leu Cys Leu Thr Ser Leu Gln Val
185 190 195
His Arg Val Ala Arg Arg His Cys Gln Arg Met Asp Thr Val Thr
200 205 210
Met Lys Ala Leu Ala Leu Leu Ala Asp Leu His Pro Ser Val Arg
215 220 225
Gln Arg Cys Leu Ile Gln Gln Lys Arg Arg Arg His Arg Ala Thr
230 235 240
Arg Lys Ile Gly Ile Ala Ile Ala Thr Phe Leu Ile Cys Phe Ala
245 250 255
Pro Tyr Val Met Thr Arg Leu Ala Glu Leu Val Pro Phe Val Thr
260 265 270
Val Asn Ala Gln Trp Gly Ile Leu Ser Lys Cys Leu Thr Tyr Ser
275 280 285
Lys Ala Val Ala Asp Pro Phe Thr Tyr Ser Leu Leu Arg Arg Pro
290 295 300
Phe Arg Gln Val Leu Ala Gly Met Val His Arg Leu Leu Lys Arg
305 310 315
Thr Pro Arg Pro Ala Ser Thr His Asp Ser Ser Leu Asp Val Ala
320 325 330
Gly Met Val His Gln Leu Leu Lys Arg Thr Pro Arg Pro Ala Ser
335 340 345
Thr His Asn Gly Ser Val Asp Thr Glu Asn Asp Ser Cys Leu Gln
350 355 360
Gln Thr His

<210> 32
<211> 308
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472019CD1

<400> 32
Met Ala Met Asp Asn Val Thr Ala Val Phe Gln Phe Leu Leu Ile

```
  1               5                  10                  15
Gly Ile Ser Asn Tyr Pro Gln Trp Arg Asp Thr Phe Phe Thr Leu
             20                  25                  30
Val Leu Ile Ile Tyr Leu Ser Thr Leu Leu Gly Asn Gly Phe Met
             35                  40                  45
Ile Phe Leu Ile His Phe Asp Pro Asn Leu His Thr Pro Ile Tyr
             50                  55                  60
Phe Phe Leu Ser Asn Leu Ser Phe Leu Asp Leu Cys Tyr Gly Thr
             65                  70                  75
Ala Ser Met Pro Gln Ala Leu Val His Cys Phe Ser Thr His Pro
             80                  85                  90
Tyr Leu Ser Tyr Pro Arg Cys Leu Ala Gln Thr Ser Val Ser Leu
             95                  100                 105
Ala Leu Ala Thr Ala Glu Cys Leu Leu Leu Ala Ala Met Ala Tyr
            110                 115                 120
Asp Arg Val Val Ala Ile Ser Asn Pro Leu Arg Tyr Ser Val Val
            125                 130                 135
Met Asn Gly Pro Val Cys Val Cys Leu Val Ala Thr Ser Trp Gly
            140                 145                 150
Thr Ser Leu Val Leu Thr Ala Met Leu Ile Leu Ser Leu Arg Leu
            155                 160                 165
His Phe Cys Gly Ala Asn Val Ile Asn His Phe Ala Cys Glu Ile
            170                 175                 180
Leu Ser Leu Ile Lys Leu Thr Cys Ser Asp Thr Ser Leu Asn Glu
            185                 190                 195
Phe Met Ile Leu Ile Thr Ser Ile Phe Thr Leu Leu Leu Pro Phe
            200                 205                 210
Gly Phe Val Leu Leu Ser Tyr Ile Arg Ile Ala Met Ala Ile Ile
            215                 220                 225
Arg Ile Arg Ser Leu Gln Gly Arg Leu Lys Ala Phe Thr Thr Cys
            230                 235                 240
Gly Ser His Leu Thr Val Val Thr Ile Phe Tyr Gly Ser Ala Ile
            245                 250                 255
Ser Met Tyr Met Lys Thr Gln Ser Lys Ser Tyr Pro Asp Gln Asp
            260                 265                 270
Lys Phe Ile Ser Val Phe Tyr Gly Ala Leu Thr Pro Met Leu Asn
            275                 280                 285
Pro Leu Ile Tyr Ser Leu Arg Lys Lys Asp Val Lys Arg Ala Ile
            290                 295                 300
Arg Lys Val Met Leu Lys Arg Thr
            305
```

<210> 33
<211> 343
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472021CD1

<400> 33

```
Met His Phe Leu Pro Thr Val Phe Gly Phe Leu Asn Arg Val Thr
  1               5                  10                  15
Leu Gly Ile Phe Arg Glu Thr Met Val Asn Leu Thr Ser Met Ser
             20                  25                  30
Gly Phe Leu Leu Met Gly Phe Ser Asp Glu Arg Lys Leu Gln Ile
             35                  40                  45
Leu His Ala Leu Val Phe Leu Val Thr Tyr Leu Leu Ala Leu Thr
             50                  55                  60
Gly Asn Leu Leu Ile Ile Thr Ile Ile Thr Val Asp Arg Arg Leu
             65                  70                  75
His Ser Pro Met Tyr Tyr Phe Leu Lys His Leu Ser Leu Leu Asp
             80                  85                  90
Leu Cys Phe Ile Ser Val Thr Val Pro Gln Ser Ile Ala Asn Ser
             95                  100                 105
Leu Met Gly Asn Gly Tyr Ile Ser Leu Val Gln Cys Ile Leu Gln
```

```
                110                 115                 120
Val Phe Phe Phe Ile Ala Leu Ala Ser Ser Glu Val Ala Ile Leu
                125                 130                 135
Thr Val Met Ser Tyr Asp Arg Tyr Ala Ala Ile Cys Gln Pro Leu
                140                 145                 150
His Tyr Glu Thr Ile Met Asp Pro Arg Ala Cys Arg His Ala Val
                155                 160                 165
Ile Ala Val Trp Ile Ala Gly Gly Leu Ser Gly Leu Met His Ala
                170                 175                 180
Ala Ile Asn Phe Ser Ile Pro Leu Cys Gly Lys Arg Val Ile His
                185                 190                 195
Gln Phe Phe Cys Asp Val Pro Gln Met Leu Lys Leu Ala Cys Ser
                200                 205                 210
Tyr Glu Phe Ile Asn Glu Ile Ala Leu Ala Ala Phe Thr Thr Ser
                215                 220                 225
Ala Ala Phe Ile Cys Leu Ile Ser Ile Val Leu Ser Tyr Ile Arg
                230                 235                 240
Ile Phe Ser Thr Val Leu Arg Ile Pro Ser Ala Glu Gly Arg Thr
                245                 250                 255
Lys Val Phe Ser Thr Cys Leu Pro His Leu Phe Val Ala Thr Phe
                260                 265                 270
Phe Leu Ser Ala Ala Gly Phe Glu Phe Leu Arg Leu Pro Ser Asp
                275                 280                 285
Ser Ser Ser Thr Val Asp Leu Val Phe Ser Val Phe Tyr Thr Val
                290                 295                 300
Ile Pro Pro Thr Leu Asn Pro Val Ile Tyr Ser Leu Arg Asn Asp
                305                 310                 315
Ser Met Lys Ala Ala Leu Arg Lys Met Leu Ser Lys Glu Glu Leu
                320                 325                 330
Pro Gln Arg Lys Met Cys Leu Lys Ala Met Phe Lys Leu
                335                 340
```

<210> 34
<211> 323
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472009CD1

<400> 34

```
Met Trp Gln Lys Asn Gln Thr Ser Leu Ala Asp Phe Ile Leu Glu
  1               5                  10                  15
Gly Leu Phe Asp Asp Ser Leu Thr His Leu Phe Leu Phe Ser Leu
                 20                  25                  30
Thr Met Val Val Phe Leu Ile Ala Val Ser Gly Asn Thr Leu Thr
                 35                  40                  45
Ile Leu Leu Ile Cys Ile Asp Pro Gln Leu His Thr Pro Met Tyr
                 50                  55                  60
Phe Leu Leu Ser Gln Leu Ser Leu Met Asp Leu Met His Val Ser
                 65                  70                  75
Thr Thr Ile Leu Lys Met Ala Thr Asn Tyr Leu Ser Gly Lys Lys
                 80                  85                  90
Ser Ile Ser Phe Val Gly Cys Ala Thr Gln His Phe Leu Tyr Leu
                 95                 100                 105
Cys Leu Gly Gly Ala Glu Cys Phe Leu Leu Ala Val Met Ser Tyr
                110                 115                 120
Asp Arg Tyr Val Ala Ile Cys His Pro Leu Arg Tyr Ala Val Leu
                125                 130                 135
Met Asn Lys Lys Val Gly Leu Met Met Ala Val Met Ser Trp Leu
                140                 145                 150
Gly Ala Ser Val Asn Ser Leu Ile His Met Ala Ile Leu Met His
                155                 160                 165
Phe Pro Phe Cys Gly Pro Arg Lys Val Tyr His Phe Tyr Cys Glu
                170                 175                 180
Phe Pro Ala Val Val Lys Leu Val Cys Gly Asp Ile Thr Val Tyr
```

```
                185                 190                 195
Glu Thr Thr Val Tyr Ile Ser Ser Ile Leu Leu Leu Leu Pro Ile
                200                 205                 210
Phe Leu Ile Ser Thr Ser Tyr Val Phe Ile Leu Gln Ser Val Ile
                215                 220                 225
Gln Met Arg Ser Ser Gly Ser Lys Arg Asn Ala Phe Ala Thr Cys
                230                 235                 240
Gly Ser His Leu Thr Val Val Ser Leu Trp Phe Gly Ala Cys Ile
                245                 250                 255
Phe Ser Tyr Met Arg Pro Arg Ser Gln Cys Thr Leu Leu Gln Asn
                260                 265                 270
Lys Val Gly Ser Val Phe Tyr Ser Ile Ile Thr Pro Thr Leu Asn
                275                 280                 285
Ser Leu Ile Tyr Thr Leu Arg Asn Lys Asp Val Ala Lys Ala Leu
                290                 295                 300
Arg Arg Val Leu Arg Arg Asp Val Ile Thr Gln Cys Ile Gln Arg
                305                 310                 315
Leu Gln Leu Trp Leu Pro Arg Val
                320
```

<210> 35
<211> 299
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472010CD1

<400> 35

```
Met Glu Leu Glu Gly Asp Phe Leu Gly Ser Val Gly Glu Leu Gly
  1                 5                  10                  15
Gln Val Ile Gln Thr Cys Ser Gly Ile Tyr Val Phe Thr Val Val
                 20                  25                  30
Gly Asn Leu Gly Leu Ile Thr Leu Ile Gly Ile Asn Pro Ser Leu
                 35                  40                  45
His Thr Pro Met Tyr Phe Phe Leu Phe Asn Leu Ser Phe Ile Asp
                 50                  55                  60
Leu Cys Tyr Ser Cys Val Phe Thr Pro Lys Met Leu Asn Asp Phe
                 65                  70                  75
Val Ser Glu Ser Ile Ile Ser Tyr Val Gly Cys Met Thr Gln Leu
                 80                  85                  90
Phe Phe Phe Cys Phe Phe Val Asn Ser Glu Cys Tyr Val Leu Val
                 95                 100                 105
Ser Met Ala Tyr Asp Arg Tyr Val Ala Ile Cys Asn Pro Leu Leu
                110                 115                 120
Tyr Met Val Thr Met Ser Pro Arg Val Cys Phe Leu Leu Met Phe
                125                 130                 135
Gly Ser Tyr Val Val Gly Phe Ala Gly Ala Met Ala His Thr Gly
                140                 145                 150
Ser Met Leu Arg Leu Thr Phe Cys Asp Ser Asn Val Ile Asp His
                155                 160                 165
Tyr Leu Cys Asp Val Leu Pro Leu Leu Gln Leu Ser Cys Thr Ser
                170                 175                 180
Thr His Val Ser Glu Leu Val Phe Phe Ile Val Val Gly Val Ile
                185                 190                 195
Thr Met Leu Ser Ser Ile Ser Ile Val Ile Ser Tyr Ala Leu Ile
                200                 205                 210
Leu Ser Asn Ile Leu Cys Ile Pro Ser Ala Glu Gly Arg Ser Lys
                215                 220                 225
Ala Phe Ser Thr Trp Gly Ser His Ile Ile Ala Val Ala Leu Phe
                230                 235                 240
Phe Gly Ser Gly Thr Phe Thr Tyr Leu Thr Thr Ser Phe Pro Gly
                245                 250                 255
Ser Met Asn His Gly Arg Phe Ala Ser Val Phe Tyr Thr Asn Val
                260                 265                 270
Val Pro Met Leu Asn Pro Ser Ile Tyr Ser Leu Arg Asn Lys Asp
```

```
                275                 280                 285
Asp Lys Leu Ala Leu Gly Lys Thr Leu Lys Arg Val Leu Phe
                290                 295

<210> 36
<211> 307
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472011CD1

<400> 36
Met Glu Thr Gly Asn Leu Thr Trp Val Ser Asp Phe Val Phe Leu
  1               5                  10                  15
Gly Leu Ser Gln Thr Arg Glu Leu Gln Arg Phe Leu Phe Leu Met
                20                  25                  30
Phe Leu Phe Val Tyr Ile Thr Thr Val Met Gly Asn Ile Leu Ile
                35                  40                  45
Ile Ile Thr Val Thr Ser Asp Ser Gln Leu His Thr Pro Met Tyr
                50                  55                  60
Phe Leu Leu Arg Asn Leu Ala Val Leu Asp Leu Cys Phe Ser Ser
                65                  70                  75
Val Thr Ala Pro Lys Met Leu Val Asp Leu Leu Ser Glu Lys Lys
                80                  85                  90
Thr Ile Ser Tyr Gln Gly Cys Met Gly Gln Ile Phe Phe Phe His
                95                 100                 105
Phe Leu Gly Gly Ala Met Val Phe Phe Leu Ser Val Met Ala Phe
               110                 115                 120
Asp Arg Leu Ile Ala Ile Ser Arg Pro Leu Arg Tyr Val Thr Val
               125                 130                 135
Met Asn Thr Gln Leu Trp Val Gly Leu Val Val Ala Thr Trp Val
               140                 145                 150
Gly Gly Phe Val His Ser Ile Val Gln Leu Ala Leu Met Leu Pro
               155                 160                 165
Leu Pro Phe Cys Gly Pro Asn Ile Leu Asp Asn Phe Tyr Cys Asp
               170                 175                 180
Val Pro Gln Val Leu Arg Leu Ala Cys Thr Asp Thr Ser Leu Leu
               185                 190                 195
Glu Phe Leu Lys Ile Ser Asn Ser Gly Leu Leu Asp Val Val Trp
               200                 205                 210
Phe Phe Leu Leu Leu Met Ser Tyr Leu Phe Ile Leu Val Met Leu
               215                 220                 225
Arg Ser His Pro Gly Glu Ala Arg Arg Lys Ala Ala Ser Thr Cys
               230                 235                 240
Thr Thr His Ile Ile Val Val Ser Met Ile Phe Val Pro Ser Ile
               245                 250                 255
Tyr Leu Tyr Ala Arg Pro Phe Thr Pro Phe Pro Met Asp Lys Leu
               260                 265                 270
Val Ser Ile Gly His Thr Val Met Thr Pro Met Leu Asn Pro Met
               275                 280                 285
Ile Tyr Thr Leu Arg Asn Gln Asp Met Gln Ala Ala Val Arg Arg
               290                 295                 300
Leu Gly Arg His Arg Leu Val
               305

<210> 37
<211> 314
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472012CD1

<400> 37
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```
Met Asp Asn Ser Asn Trp Thr Ser Val Ser His Phe Val Leu Leu
  1               5                  10                  15
Gly Ile Ser Thr His Pro Glu Glu Gln Ile Pro Leu Phe Leu Val
             20                  25                  30
Phe Ser Leu Met Tyr Ala Ile Asn Ile Ser Gly Asn Leu Ala Ile
             35                  40                  45
Ile Thr Leu Ile Leu Ser Ala Pro Arg Leu His Ile Pro Met Tyr
             50                  55                  60
Ile Phe Leu Ser Asn Leu Ala Leu Thr Asp Ile Cys Phe Thr Ser
             65                  70                  75
Thr Thr Val Pro Lys Met Leu Gln Ile Ile Phe Ser Pro Thr Lys
             80                  85                  90
Val Ile Ser Tyr Thr Gly Cys Leu Ala Gln Thr Tyr Phe Phe Ile
             95                 100                 105
Cys Phe Ala Val Met Glu Asn Phe Ile Leu Ala Val Met Ala Tyr
            110                 115                 120
Asp Arg Tyr Ile Ala Ile Cys His Pro Phe His Tyr Thr Met Ile
            125                 130                 135
Leu Thr Arg Met Leu Cys Val Lys Met Val Val Met Cys His Ala
            140                 145                 150
Leu Ser His Leu His Ala Met Leu His Thr Phe Leu Ile Gly Gln
            155                 160                 165
Leu Ile Phe Cys Ala Asp Asn Arg Ile Pro His Phe Phe Cys Asp
            170                 175                 180
Leu Tyr Ala Leu Met Lys Ile Ser Cys Thr Ser Thr Tyr Leu Asn
            185                 190                 195
Thr Leu Met Ile His Thr Glu Gly Ala Val Val Ile Ser Gly Ala
            200                 205                 210
Leu Ala Phe Ile Thr Ala Ser Tyr Ala Cys Ile Ile Leu Val Val
            215                 220                 225
Leu Arg Ile Pro Ser Ala Lys Gly Arg Trp Lys Thr Phe Ser Thr
            230                 235                 240
Cys Gly Ser His Leu Thr Val Val Ala Ile Phe Tyr Gly Thr Leu
            245                 250                 255
Ser Trp Val Tyr Phe Arg Pro Leu Ser Ser Tyr Ser Val Thr Lys
            260                 265                 270
Gly Arg Ile Ile Thr Val Val Tyr Thr Val Val Thr Pro Met Leu
            275                 280                 285
Asn Pro Phe Ile Tyr Ser Leu Arg Asn Gly Asp Val Lys Gly Gly
            290                 295                 300
Phe Met Lys Trp Met Ser Arg Met Gln Thr Phe Phe Phe Arg
            305                 310
```

<210> 38
<211> 310
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472014CD1

<400> 38

```
Met Gly Arg Asn Asn Leu Thr Arg Pro Ser Glu Phe Ile Leu Leu
  1               5                  10                  15
Gly Leu Ser Ser Arg Pro Glu Asp Gln Lys Pro Leu Phe Ala Val
             20                  25                  30
Phe Leu Pro Ile Tyr Leu Ile Thr Val Ile Gly Asn Leu Leu Ile
             35                  40                  45
Ile Leu Ala Ile Arg Ser Asp Thr Arg Leu Gln Thr Pro Met Tyr
             50                  55                  60
Phe Phe Leu Ser Ile Leu Ser Phe Val Asp Ile Cys Tyr Val Thr
             65                  70                  75
Val Ile Ile Pro Lys Met Leu Val Asn Phe Leu Ser Glu Thr Lys
             80                  85                  90
Thr Ile Ser Tyr Gly Glu Cys Leu Thr Gln Met Tyr Phe Phe Leu
             95                 100                 105
```

```
Ala Phe Gly Asn Thr Asp Ser Tyr Leu Leu Ala Ala Met Ala Ile
                110                 115                 120
Asp Arg Tyr Val Ala Ile Cys Asn Pro Phe His Tyr Ile Thr Ile
                125                 130                 135
Met Ser His Arg Cys Cys Val Leu Leu Leu Val Leu Ser Phe Cys
                140                 145                 150
Ile Pro His Phe His Ser Leu Leu His Ile Leu Leu Thr Asn Gln
                155                 160                 165
Leu Ile Phe Cys Ala Ser Asn Val Ile His His Phe Phe Cys Asp
                170                 175                 180
Asp Gln Pro Val Leu Lys Leu Ser Cys Ser Ser His Phe Val Lys
                185                 190                 195
Glu Ile Thr Val Met Thr Glu Gly Leu Ala Val Ile Met Thr Pro
                200                 205                 210
Phe Ser Cys Ile Ile Ile Ser Tyr Leu Arg Ile Leu Ile Thr Val
                215                 220                 225
Leu Lys Ile Pro Ser Ala Ala Gly Lys Arg Lys Ala Phe Ser Thr
                230                 235                 240
Cys Gly Ser His Leu Thr Val Val Thr Leu Phe Tyr Gly Ser Ile
                245                 250                 255
Ser Tyr Val Tyr Phe Gln Pro Leu Ser Asn Tyr Thr Val Lys Asp
                260                 265                 270
Gln Ile Ala Thr Ile Ile Tyr Thr Val Leu Thr Pro Met Leu Asn
                275                 280                 285
Pro Phe Ile Tyr Ser Leu Arg Asn Lys Asp Met Lys Gln Gly Leu
                290                 295                 300
Ala Lys Leu Met His Arg Met Lys Cys Gln
                305                 310
```

<210> 39
<211> 359
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472020CD1

<400> 39

```
Met Phe Lys Ala Ile Leu Gly His Val Trp Pro Lys Asp His Gly
  1               5                  10                  15
Leu Asp Lys Leu Val Val Arg Cys Pro Arg His Thr Glu Pro Trp
                 20                  25                  30
Asn Leu Thr Gly Ile Ser Glu Phe Leu Leu Leu Gly Leu Ser Glu
                 35                  40                  45
Asp Pro Glu Leu Gln Pro Val Leu Pro Gly Leu Ser Leu Ser Met
                 50                  55                  60
Tyr Leu Val Thr Val Leu Arg Asn Leu Leu Ile Ile Leu Ala Val
                 65                  70                  75
Ser Ser Asp Ser His Leu His Thr Pro Met Cys Phe Phe Leu Ser
                 80                  85                  90
Asn Leu Cys Trp Ala Asp Ile Gly Phe Thr Ser Ala Met Val Pro
                 95                 100                 105
Lys Met Ile Val Asp Met Gln Ser His Ser Arg Val Ile Ser Tyr
                110                 115                 120
Ala Gly Cys Leu Thr Gln Met Ser Phe Phe Val Leu Phe Ala Cys
                125                 130                 135
Ile Glu Asp Met Leu Leu Thr Val Met Ala Tyr Asp Arg Phe Val
                140                 145                 150
Ala Ile Cys His Pro Leu His Tyr Pro Val Ile Met Asn Pro His
                155                 160                 165
Leu Gly Val Phe Leu Val Leu Val Ser Phe Phe Leu Ser Leu Leu
                170                 175                 180
Asp Ser Gln Leu His Ser Trp Ile Val Leu Gln Phe Thr Phe Phe
                185                 190                 195
Lys Asn Val Glu Ile Ser Asn Phe Val Cys Asp Pro Ser Gln Leu
                200                 205                 210
```

```
Leu Asn Leu Ala Cys Ser Asp Ser Val Ile Asn Ser Ile Phe Ile
                215                 220                 225
Tyr Leu Asp Ser Ile Met Phe Gly Phe Leu Pro Ile Ser Gly Ile
                230                 235                 240
Leu Leu Ser Tyr Ala Asn Asn Val Pro Ser Ile Leu Arg Ile Ser
                245                 250                 255
Ser Ser Asp Arg Lys Ser Lys Ala Phe Ser Thr Cys Gly Ser His
                260                 265                 270
Leu Ala Val Val Cys Leu Phe Tyr Gly Thr Gly Ile Gly Val Tyr
                275                 280                 285
Leu Thr Ser Ala Val Ser Pro Pro Pro Arg Asn Gly Val Val Ala
                290                 295                 300
Ser Val Met Tyr Ala Val Val Thr Pro Met Leu Asn Pro Phe Ile
                305                 310                 315
Tyr Ser Leu Arg Asn Arg Asp Ile Gln Ser Ala Leu Trp Arg Leu
                320                 325                 330
Arg Ser Arg Thr Val Glu Ser His Asp Leu Leu Ser Gln Asp Leu
                335                 340                 345
Leu His Pro Phe Ser Cys Val Gly Glu Lys Gly Gln Pro His
                350                 355
```

<210> 40
<211> 936
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 104941CB1

<400> 40
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atggagataa agaactacag cagcagcacc tcaggcttca tcctcctggg cctctcttcc 60
aaccctcagc tgcagaaacc tctctttgcc atcttcctca tcatgtacct gctcgctgcg 120
gtggggaatg tgctcatcat cccggccatc tactctgacc ccaggctcca cacccctatg 180
tacttttttc tcagcaactt gtctttcatg gatatctgct tcacaacagt catagtgcct 240
aagatgctgg tgaatttttct atcagagaca aaggttatct cctatgtggg ctgcctggcc 300
cagatgtact tctttatggc atttgggaac actgacagct acctgctggc ctctatggcc 360
atcgaccggc tggtggccat ctgcaacccc ttacactatg atgtggttat gaaaccacgg 420
cattgcctgc tcatgctatt gggttcttgc agcatctccc acctacattc cctgttccgc 480
gtgctactta tgtctcgctt gtctttctgt gcctctcaca tcattaagca ctttttctgt 540
gacacccagc ctgtgctaaa gctctcctgc tctgacacat cctccagcca gatggtggtg 600
atgactgaga ccttagctgt cattgtgacc cccttcctgt gtatcatctt ctcctacctg 660
cgaatcatgg tcactgtgct cagaatcccc tctgcagccg ggaagtggaa ggccttctct 720
acctgtggct cccacctcac tgcagtagcc cttttctatg ggagtattat ttatgtctat 780
tttaggcccc tgtccatgta ctcagtggtt agggaccggg tagccacagt tatgtacaca 840
gtagtgacac ccatgctgaa ccctttcatc tacagcctga ggaacaaaga tatgaagagg 900
ggtttgaaga aattacagga cagaatttac cggtaa                          936
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<210> 41
<211> 3365
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1499408CB1

<400> 41
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atggaccagc cagaggcccc ctgctccagc acggggccgc gcctcgcggt ggcccgcgag 60
ctgctcctgg ctgcgctgga ggaactgagc caagagcagc tgaagcgctt ccgccacaag 120
ctgcgcgacg tgggcccgga cggacgcagc atcccgtggg ggcggctgga gcgcgcggac 180
gccgtggacc tcgcggagca gctggcccag ttctacggcc cggagcctgc cctggaggtg 240
gcccgcaaga ccctcaagag ggcggacgcg cgcgacgtgg cggcgcagct ccaggagcgg 300
cggctgcagc ggctcgggct cggctccggg acgctgctct ccgtgtccga gtacaagaag 360
aagtaccggg agcacgtgct gcagctgcac gctcgggtga aggagaggaa cgcccgctcc 420
gtgaagatca ccaagcgctt caccaagctg ctcatcgcgc ccgagagcgc cgccccggag 480
gaggcgctgg ggcccgcgga agagcctgag ccggggcgcg cgcggcgctc ggacacgcac 540
```

actttcaacc gcctcttccg ccgcgacgag gagggccggc ggccgctgac cgtggtgctg 600
cagggcccgg cgggcatcgg caagaccatg gcggccaaaa agatcctgta cgactgggcg 660
gcgggcaagc tgtaccaggg ccaggtggac ttcgccttct tcatgccctg cggcgagctg 720
ctggagaggc cgggcacgcg cagcctggct gacctgatcc tggaccagtg ccccgaccgc 780
ggcgcgccgg tgccgcagat gctggcccag ccgcagcggc tgctcttcat cctggacggc 840
gcggacgagc tgccggcgct ggggggcccc gaggccgcgc cctgcacaga ccccttcgag 900
gcggcgagcg gcgcgcgggt gctaggcggg ctgctgagca aggcgctgct gcccacggcc 960
ctcctgctgg tgaccacgcg cgccgccgcc cccgggaggc tgcagggccg cctgtgttcc 1020
ccgcagtgcg ccgaggtgcg cggcttctcc gacaaggaca agaagaagta tttctacaag 1080
ttcttccggg atgagaggag ggccgagcgc gcctaccgct tcgtgaagga gaacgagacg 1140
ctgttcgcgc tgtgcttcgt gcccttcgtg tgctggatcg tgtgcaccgt gctgcgccag 1200
cagctggagc tcggtcggga cctgtcgcgc acgtccaaga ccaccacgtc agtgtacctg 1260
cttttcatca ccagcgttct gagctcggct ccggtagccg acgggccccg gttgcagggc 1320
gacctgcgca atctgtgccg cctggcccgc gagggcgtcc tcggacgcag ggcgcagttt 1380
gccgagaagg aactggagca actggagctt cgtggctcca aagtgcagac gctgtttctc 1440
agcaaaaagg agctgccggg cgtgctggag acagaggtca cctaccagtt catcgaccag 1500
agcttccagg agttcctcgc ggcactgtcc tacctgctgg aggacggcgg ggtgcccagg 1560
accgcggctg gcggcgttgg gacactcctg cgtggggacg cccagccgca cagccacttg 1620
gtgctcacca cgcgcttcct cttcggactg ctgagcgcgg agcggatgcg cgacatcgag 1680
cgccacttcg gctgcatggt ttcagagcgt gtgaagcagg aggccctgcg gtgggtgcag 1740
ggacagggac agggctgccc cggagtggca ccagaggtga ccgagggggc caaagggctc 1800
gaggacaccg aagagccaga ggaggaggag gagggagagg agcccaacta cccactggag 1860
ttgctgtact gcctgtacga gacgcaggag gacgcgtttg tgcgccaagc cctgtgccgg 1920
ttcccggagc tggcgctgca gcgagtgcgc ttctgccgca tggacgtggc tgttctgagc 1980
tactgcgtga ggtgctgccc tgctggacag gcactgcggc tgatcagctg cagattggtt 2040
gctgcgcagg agaagaagaa gaagagcctg gggaagcggc tccaggccag cctgggtggc 2100
ggcagttctc aaggcaccac aaaacaactg ccagcctccc ttcttcatcc actctttcag 2160
gcaatgactg acccactgtg ccatctgagc agcctcacgc tgtcccactg caaactccct 2220
gacgcggtct gccgagacct ttctgaggcc ctgagggcag cccccgcact gacggagctg 2280
ggcctcctcc acaacaggct cagtgaggcg ggactgcgta tgctgagtga gggcctagcc 2340
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cagtacctgg tgggtatgct tcggcagagc cccgccctga ccaccctgga tctcagcggc 2460
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<213> Homo sapiens

<220>
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<223> Incyte ID No: 3168839CB1

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<211> 2124
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3291235CB1

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<211> 942
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 7472001CB1

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<211> 1197
<212> DNA
<213> Homo sapiens

<220>
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<210> 46
<211> 1110
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7472004CB1

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gccatgaggt ctgcaattaa catcctcctt gccagcctag cttttgcaga catgttgctt 240

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<210> 47
<211> 582
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7475687CT1

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<210> 48
<211> 519
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
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<210> 49
<211> 663
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7477933CT1

<400> 49

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tag 663

<210> 50
<211> 911
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 7475164CT1

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<210> 51
<211> 332
<212> DNA
<213> Homo sapiens

<220>
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<210> 52
<211> 538
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7475252CT1

<400> 52

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<210> 53
<211> 279
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 7927572CT1

<400> 53
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<210> 54
<211> 291
<212> DNA
<213> Homo sapiens

<220>
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<400> 54
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<210> 55
<211> 402
<212> DNA
<213> Homo sapiens

<220>
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<210> 56
<211> 639
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<212> DNA
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<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<223> Incyte ID No: 7472021CB1

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<211> 972
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No: 7472009CB1

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<212> DNA
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<212> DNA
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<212> DNA
<213> Homo sapiens

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(19) World Intellectual Property Organization
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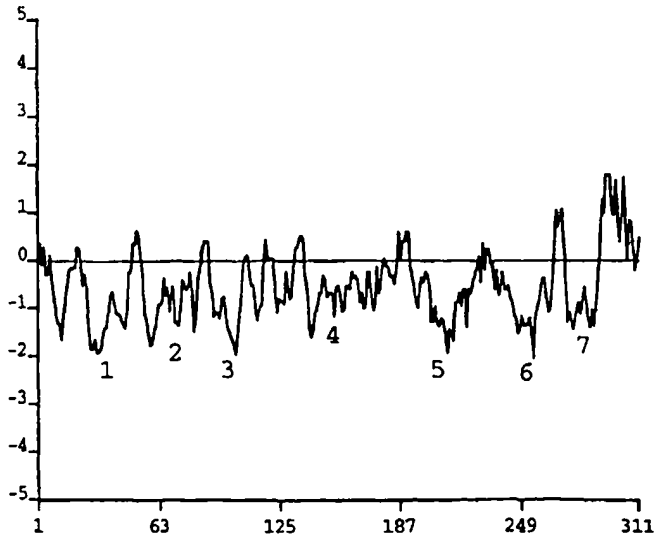
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: G-PROTEIN COUPLED RECEPTORS



SEQ ID NO:1
(Incyte ID No. 104941CD1)

(57) Abstract: The invention provides human G-protein coupled receptors (GCREC) and polynucleotides which identify and encode GCREC. The invention also provides expression vectors, host, cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with aberrant expression of GCREC.

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patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
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INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/US 00/33382

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/705 C12N15/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, WPI Data, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 17585 A (UNIV COLUMBIA) 15 October 1992 (1992-10-15) claims 37,5; figure 10 ---	1-28
X	BUCK L ET AL: "A NOVEL MULTIGENE FAMILY MAY ENCODE ODORANT RECEPTORS: A MOLECULAR BASIS FOR ODOR RECOGNITION" CELL,US,CELL PRESS, CAMBRIDGE, NA, vol. 65, 5 April 1991 (1991-04-05), pages 175-187, XP002029935 ISSN: 0092-8674 the whole document --- -/--	1-28

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 May 2001	23.08.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Meyer, W

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MCDONALD TERRY ET AL: "Identification and cloning of an orphan G protein-coupled receptor of the glycoprotein hormone receptor subfamily." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 247, no. 2, 18 June 1998 (1998-06-18), pages 266-270, XP000999191 ISSN: 0006-291X the whole document ---	1-28
A	GONG Z ET AL: "Rapid identification and isolation of zebrafish cDNA clones" GENE: AN INTERNATIONAL JOURNAL ON GENES AND GENOMES,GB,ELSEVIER SCIENCE PUBLISHERS, BARKING, vol. 201, no. 1-2, 12 November 1997 (1997-11-12), pages 87-98, XP004126460 ISSN: 0378-1119 abstract ---	1-28
A	STADEL J M ET AL: "Orphan G protein-coupled receptors: a neglected opportunity for pioneer drug discovery" TRENDS IN PHARMACOLOGICAL SCIENCES,GB,ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 18, no. 11, 1 November 1997 (1997-11-01), pages 430-437, XP004099345 ISSN: 0165-6147 abstract; table 1 ---	1-28
A	O'DOWD B F ET AL: "DISCOVERY OF THREE NOVEL G-PROTEIN-COUPLED RECEPTOR GENES" GENOMICS,ACADEMIC PRESS, SAN DIEGO,US, vol. 47, no. 2, 15 January 1998 (1998-01-15), pages 310-313, XP000863786 ISSN: 0888-7543 abstract ---	1-28
A	MARCHESE A ET AL: "Novel GPCRs and their endogenous ligands: expanding the boundaries of physiology and pharmacology" TRENDS IN PHARMACOLOGICAL SCIENCES,GB,ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 20, no. 9, 1 September 1999 (1999-09-01), pages 370-375, XP004178194 ISSN: 0165-6147 abstract ---	1-28
	-/--	

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INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/US 00/33382

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	LEE DENNIS K ET AL: "Cloning and characterization of additional members of the G protein-coupled receptor family." BIOCHIMICA ET BIOPHYSICA ACTA., vol. 1490, no. 3, 29 February 2000 (2000-02-29), pages 311-323, XP000999198 ISSN: 0006-3002 the whole document ---	1-28
P,X	ROUQUIER SYLVIE ET AL: "The olfactory receptor gene repertoire in primates and mouse: Evidence for reduction of the functional fraction in primates." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 97, no. 6, 14 March 2000 (2000-03-14), pages 2870-2874, XP002168634 March 14, 2000 ISSN: 0027-8424 the whole document -----	1-28

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/33382

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18, 21, 24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

partially 1-28

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: partially 1-28

   G protein-coupled receptor as characterized by SEQ.ID.1, its corresponding DNA (SEQ.ID.40) and the use thereof.

2. Claims: partially 1-28

   G protein-coupled receptor as characterized by SEQ.ID.2, its corresponding DNA (SEQ.ID.41) and the use thereof.

3. Claims: partially 1-28

   G protein-coupled receptor as characterized by SEQ.ID.3, its corresponding DNA (SEQ.ID.42) and the use thereof.

4. Claims: partially 1-28

   G protein-coupled receptor as characterized by SEQ.ID.4, its corresponding DNA (SEQ.ID.43) and the use thereof.

5. Claims: partially 1-28

   G protein-coupled receptor as characterized by SEQ.ID.5, its corresponding DNA (SEQ.ID.44) and the use thereof.

6. Claims: partially 1-28

   G protein-coupled receptor as characterized by SEQ.ID.6, its corresponding DNA (SEQ.ID.45) and the use thereof.

7. Claims: partially 1-28

   G protein-coupled receptor as characterized by SEQ.ID.7, its corresponding DNA (SEQ.ID.46) and the use thereof.

8. Claims: partially 1-28

   G protein-coupled receptor as characterized by SEQ.ID.8, its corresponding DNA (SEQ.ID.47) and the use thereof.

9. Claims: partially 1-28

   G protein-coupled receptor as characterized by SEQ.ID.9, its corresponding DNA (SEQ.ID.48) and the use thereof.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.10, its corresponding DNA (SEQ.ID.49) and the use thereof.

11. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.11, its corresponding DNA (SEQ.ID.50) and the use thereof.

12. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.12, its corresponding DNA (SEQ.ID.51) and the use thereof.

13. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.13, its corresponding DNA (SEQ.ID.52) and the use thereof.

14. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.14, its corresponding DNA (SEQ.ID.53) and the use thereof.

15. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.15, its corresponding DNA (SEQ.ID.54) and the use thereof.

16. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.16, its corresponding DNA (SEQ.ID.55) and the use thereof.

17. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.17, its corresponding DNA (SEQ.ID.56) and the use thereof.

18. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.18 its corresponding DNA (SEQ.ID.57) and the use thereof.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

19. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.19, its corresponding DNA (SEQ.ID.58) and the use thereof.

20. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.20, its corresponding DNA (SEQ.ID.59) and the use thereof.

21. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.21, its corresponding DNA (SEQ.ID.60) and the use thereof.

22. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.22, its corresponding DNA (SEQ.ID.61) and the use thereof.

23. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.23, its corresponding DNA (SEQ.ID.62) and the use thereof.

24. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.24, its corresponding DNA (SEQ.ID.63) and the use thereof.

25. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.25, its corresponding DNA (SEQ.ID.64) and the use thereof.

26. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.26, its corresponding DNA (SEQ.ID.65) and the use thereof.

27. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.27, its corresponding DNA (SEQ.ID.66) and the use thereof.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

28. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.28, its corresponding DNA (SEQ.ID.67) and the use thereof.

29. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.29, its corresponding DNA (SEQ.ID.68) and the use thereof.

30. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.30, its corresponding DNA (SEQ.ID.69) and the use thereof.

31. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.31, its corresponding DNA (SEQ.ID.70) and the use thereof.

32. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.32, its corresponding DNA (SEQ.ID.71) and the use thereof.

33. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.33, its corresponding DNA (SEQ.ID.72) and the use thereof.

34. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.34, its corresponding DNA (SEQ.ID.73) and the use thereof.

35. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.35, its corresponding DNA (SEQ.ID.74) and the use thereof.

36. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.36, its corresponding DNA (SEQ.ID.75) and the use thereof.

37. Claims: partially 1-28

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

G protein-coupled receptor as characterized by SEQ.ID.37, its corresponding DNA (SEQ.ID.76) and the use thereof.

38. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.38, its corresponding DNA (SEQ.ID.77) and the use thereof.

39. Claims: partially 1-28

G protein-coupled receptor as characterized by SEQ.ID.39, its corresponding DNA (SEQ.ID.78) and the use thereof.

INTERNATIONAL SEARCH REPORT

.ormation on patent family members

Interm nal Application No
PCT/US 00/33382

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9217585 A	15-10-1992	AU 669107 B	30-05-1996
		AU 1796192 A	02-11-1992
		CA 2106847 A	06-10-1992
		EP 0578784 A	19-01-1994
		JP 6509702 T	02-11-1994